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CONTENTS

Page

A Mid-Brain Syndrome following Head Injury
Michael Kremer, W. Ritchie Russell, and G. E. Smyth 49

A Clinico-Pathological Report on Unusual Cases of Chronic Encephalitis
William R. Rosanoff 61

Sensory Disturbances Occurring in Sciatica due to Intervertebral Disc Protrusions: Some Observations on the Fifth Lumbar and First Sacral Dermatomes
Murray A. Falconer, Gavin L. Glasgow, and David S. Cole 72

An Outbreak of Atropine Poisoning D. N. Parlett 85

The Effect of Reinnervation on Collagen Formation in Degenerating Sciatic Nerves of Rabbits
M. Abercrombie and M. L. Johnson 89

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A MID-BRAIN SYNDROME FOLLOWING HEAD INJURY

BY

MICHAEL KREMER, W. RITCHIE RUSSELL, and G. E. SMYTH

(RECEIVED 6TH DECEMBER, 1946)

HÆMORRHAGIC lesions of the brain stem are not infrequently found in fatal cases of accidental head injury. Duret (1878, 1919) emphasized their importance, and showed that they are easily produced in experimental animals. Berner (1930) and Courville (1945) also considered them to be an important cause of death, and it is clear that only a very few patients who recover from a head injury are found to have the clinical signs of severe brain-stem injury. Transient signs of brain-stem injury are, however, not uncommon, and may consist of pupillary and oculo-motor abnormalities or even decerebrate rigidity, while Denny-Brown (1941) has described cases showing delayed collapse after head injury with clinical features indicating bulbar involvement.

A few severe cases of mid-brain injury have previously been reported, one of the most striking being by Sachs (1930). The purpose of this paper is to draw attention to a rare type of case in which there is severe and permanent motor disability, probably caused by damage to the mid-brain. Air encephalography carried out in two of the cases showed dilatation of the aqueduct of Sylvius. The nine cases here described were patients in the Military Hospital for Head Injuries, Oxford, and represented a proportion of about one in 700 of the cases of accidental head injury admitted.

Case Reports

Case 1.—A driver, aged 34, met with a road accident on Aug. 24, 1944. Two and a half hours later he was unconscious, with constricted pupils, spasticity of all limbs, extensor plantar responses, and trismus. The pulse was 92 per minute, respiration 20 per minute, the blood pressure 128/76 mm. Hg. On the following morning (9 hours after the injury) the temperature rose to 105·2° F., but fell to 102° F. some hours later. Spasticity had by now become more marked. Radiographs of the skull did not disclose any evidence of fracture. On the second day a " tonic fit " occurred, affecting the right arm and leg, but no further details are available. During the next twelve days he was very restless, " thrashed about with his legs whenever disturbed," and ran a constant temperature at about 102° F., which once reached 105·6° F. Thereafter the fever subsided. From Sept. 18 the stupor lessened and the patient began to swallow soft food. At times he had fits of choking. Spasticity diminished but the plantar responses remained extensor. All voluntary movements were noted as " very jerky." By now he would obey simple commands, but he made no attempt to speak. Frequent and severe sweats were noticed, which appeared to cause great irritation of the skin, for he would rub and scratch himself with such violence that restraint was necessary. On examination on Oct. 17, 1944, it was found that the patient's general condition was fair. He was restless and speechless.

CRANIAL NERVES.—Visual acuity was not measured but he could certainly see. Visual fields and fundi were normal. The right pupil was 5 mm. in diameter, the left 4 mm., both being circular and reacting promptly to light but through a small range. External ocular movements were full, with no nystagmus. There was slight right ptosis. Cranial nerves were otherwise normal, but there was considerable dysphagia.

MOTOR FUNCTIONS.—There was slight spastic weakness of the right arm and leg. Tendon reflexes were all increased, more particularly on the right, and both plantar reflexes were extensor. Abdominal reflexes were present. The cerebrospinal fluid was clear, under a pressure of 140 mm. of water, and contained 45 mg. per cent. of protein and 6 cells per c.mm. An electro-encephalogram showed the presence of generalized medium-voltage slow waves, but no evidence of a focal lesion. The patient remained speechless, incontinent and, at times, violent until the middle of November.

By Dec. 1 the mental state had improved considerably. Speech had returned, but was so dysarthric as to be almost unintelligible. The voice was produced with great effort. The tone was high-pitched, monotonous, and curiously hissing in quality. Words were slurred and scanned, but vowels were even more distorted than consonants. The expression was fixed and fatuous, and the mood appeared happy and childish. He took little interest in his surroundings, and was poorly in touch with current events. Information obtained from his wife showed that previously he had been a highly intelligent and successful business man of stable and cheerful disposition. The photographs in Fig. 2 (see p. 54-5) were extracted from a cinematograph film and give some idea of the motor disorder and loss of balance. He

adopted, when sitting, a fixed bodily posture, with the head and trunk bent slightly forward. There were irregular and inconstant fidgety movements of the limbs. He was unable to stand unaided, and attempts at walking, when supported by two persons, led to wild movements of the trunk and lower limbs, without any control of their direction or extent. There was occasional nodding tremor of the head, and frequent outbursts of rhythmic alternating flexion and extension of the right thumb and index finger at about two and a half alternations a second. At times this tremor shifted to the right ring and little finger, leaving the thumb and index at rest.

CRANIAL NERVES.—There was bilateral lid retraction, with slight internal strabismus. The pupils were semi-dilated, the right larger than the left, and a little irregular in outline. Reaction to light was brisk through a small range, and there was minimal contraction on convergence. External ocular movements were full, with no nystagmus. There was bilateral facial rigidity, with constant blepharoclonus on closing the eyes. Jaw jerk was not increased.

MOTOR FUNCTIONS.—There was no wasting. Tone was slightly increased on the right, particularly in the arm; it was of pyramidal rather than of striatal type, with no real loss of power. There was an extreme degree of ataxia of all limbs, but more on the right and more marked in the arms than in the legs. He was totally unable to execute alternating movements. The tendon jerks were markedly increased, except that the right ankle jerk was difficult to obtain, and the increase in the tendon jerks was slightly more marked on the left side than on the right. The abdominal reflexes were present. The plantar responses were both extensor. The condition remained unchanged till his transfer to another hospital on June 8, 1945. On April 14, 1945 (eight months after the injury), lumbar air-encephalography was performed. This showed a moderate dilatation of lateral ventricles but without any distortion or displacement. The aqueduct of Sylvius was considerably dilated (Fig. 1) and the fourth ventricle slightly so. The cisterna magna was enlarged, and air could be seen filling the cistern from the foramen magnun to as high as the curved line of the occipital bone. In November, 1946, his wife reported he was still unable to walk or to use his hands properly.

SUMMARY OF FINDINGS.—There was severe closed head injury with post-traumatic confusion of some three months' duration. Fever, rising on two occasions to 105° F., occurred in the first few weeks. Initially there was marked spasticity of all the limbs. The patient was anarthric and dysphagic for two months; speech returned thereafter, but was grossly dysarthric. As the spasticity lessened, an intense ataxia of all the limbs and the trunk became evident, and rhythmic coarse tremor of the right hand and fingers developed. The tendon jerks were pathologically brisk, and the plantar responses extensor. There was a moderate degree of dementia. Air encephalography showed marked dilatation of the aqueduct of Sylvius, and some increase in the size of the cisterna magna.

Case 2.—A sapper, aged 19, sustained a severe closed head injury with laceration of the scalp and fractures of both legs when a rocket bomb hit his billet on or about Dec. 16, 1944. The early notes record that he was unconscious, with small pupils, and that there was no spasticity. No early note on the temperature exists, but some days later it was normal. The pulse rate was 100 to 120 per minute, and the blood pressure 180/110 mm. Hg, but within a week both had fallen to normal levels. He was evacuated to England on Jan. 6, 1945. On examination on Jan. 6 he was found to be considerably emaciated and very inaccessible, owing to an almost total anarthria. Apparent attempts at speech produced only a harsh long-drawn-out hissing sound. Simple commands were obeyed fairly well.

CRANIAL NERVES.—Visual fields appeared full. At rest the right eye deviated downwards and outwards, whilst the left remained central. The right pupil was larger than the left; both reacted to light. The external ocular movements were very defective, for there was no upward or inward movement of the right globe and none upward or outward of the left. The defective lateral conjugate movements were accompanied by rather coarse nystagmus.

MOTOR FUNCTIONS.—The left arm was hypotonic, and the patient made no attempt to use it voluntarily. The left leg was raised with difficulty (both legs were in plaster casts). All accessible tendon jerks were brisk, the abdominal responses were present, and the plantar responses flexor. Sensibility seemed intact. The cerebrospinal fluid was under normal pressure, and the cell content and chemical analyses were normal. Radiographs of the skull showed a slight widening of the left lambdoid suture but no sign of fracture.

PROGRESS.—On Jan. 12, 1945, he was still restless and severely confused. Speech was now comprehensible, but the prolonged and harsh hissing quality of expiration persisted. Vowel sounds were much more perverted than were consonants. The peculiar character of the speech recalled the bleat of a sheep. The range of ocular movements had increased, but neither eye adducted fully. There was no convincing nystagmus, but some slow oscillations were seen on extreme lateral movement. By the beginning of March he was able to be up for most of the day. The post-traumatic amnesia was of some ten weeks' duration. His behaviour in the ward was normal. There was little evidence of intellectual deterioration, but the mood was somewhat depressed. He complained of double vision, and of uselessness of the left arm and leg. He thought his speech was normal, but that the voice lacked power. A slight bilateral ptosis, more marked on the right side, was noticeable.

Examination on May 1, 1945, showed the general condition greatly improved. A complete psychiatric examination failed to show any evidence of intellectual loss or personality change. He got about the ward well, but the left leg was weak and unsteady and the left arm

so weak and clumsy as to be almost useless. The voice was weak and low pitched, and a trace of scanning dysarthria was detectable. He himself said that, whereas formerly he could sing quite well, now the voice did not come out properly: "I can't manage the breathing, Sir."

CRANIAL NERVES.—There was an intermittent slight nodding tremor of the head at two to three oscillations a second. Slight bilateral ptosis was present as at the last examination. Pupils were equal, and reacted normally to light. Convergence was poor, and only minimal pupillary contraction occurred. External ocular movements were full, except for limitation of adduction of the left eye. Testing by means of a Hess diplopia chart showed a paresis of mixed type, i.e. affecting the right superior rectus and inferior oblique muscles and the left inferior and internal recti and superior oblique muscles, and almost certainly indicative of a nuclear lesion. An ill-sustained and inconstant nystagmus occurred on lateral and upward movement of the eyes. In involuntary and associated movement the left lower face drooped a little. The right facial nerve showed hyperexcitability on tapping the trunk just anterior to the tragus.

MOTOR FUNCTIONS.—The left arm was hypotonic and could be displaced with undue ease, but there was little or no loss of power. When the forearm and hand were not fully supported, bursts of rapid rhythmic tremor occurred in the left index and middle fingers at a rate of three or four beats a second. This tremor was a simple movement of flexion and extension. There was gross kinetic ataxia in the finger-nose test, with well-marked terminal accentuation. Individual finger movements were very slow and laboured, while alternating movements could not be executed at all. The left leg was much less hypotonic than the arm. There was no loss of power. In the heel-shin test a very coarse and irregular ataxia was evident. Wriggling of the left toes was, however, only slightly slower than on the right. There was no disturbance of motor functions in the right limbs. The gait was slightly unsteady, but with no tendency to veer to one side more than the other. The tendon reflexes were in general increased on the left side, and the abdominal reflexes were present and equal. The plantar responses were at all times difficult to assess, and varied from day to day. Both were probably pathological. There was no disturbance of sensibility. Lumbar encephalography (May 9, 1945) showed complete absence of dilatation of the lateral and third ventricles. There was an excess of air over the occipital poles. The striking abnormality was the very considerable dilatation of the aqueduct of Sylvius (Fig. 3).

SUMMARY OF FINDINGS.—This patient had a closed head injury with post-traumatic amnesia of about ten weeks. Initially there was anarthria; later a curious harsh hissing type of phonation. Finally there was only a slight scanning dysarthria, and severe and lasting hypotonia of the left limbs, with gross ataxia and inability to execute discrete and alternating movement. There was an intermittent Parkinsonian-like tremor of the fingers of the left hand. Tendon reflexes were more active on the left than the right. There was enduring diplopia from what was considered to be a nuclear ophthalmoplegia. Dilatation of the aqueduct of Sylvius was demonstrated by air encephalography.

Case 3.—A Flight-Sergeant, aged 21, was injured in an air crash on Nov. 27, 1943. He was at first deeply comatose, and there was a post-traumatic amnesia of seventeen days. Radiographs showed that he had sustained a fissured fracture of the left parietal bone. Operation was carried out, and depressed bone fragments removed. The dura had not been perforated. On regaining consciousness there was thick, indistinct speech, some disturbance of vision, and inability to control movements of the left arm and leg. The notes stated that when the left arm was held outstretched it developed a coarse clonus. On examination (Jan. 18, 1944) he was found to be fully alert and in touch with his surroundings. He was, however, markedly euphoric and disinhibited. Speech was noted as being of the kind associated with cerebellar disease.

CRANIAL NERVES.—Pupillary reactions were normal. External ocular movements were full, but on extreme lateral movement a fine nystagmus appeared. There was slight but definite left ptosis.

MOTOR FUNCTIONS.—All limbs were hypotonic, but the left side was the more affected. There was minimal weakness of the left leg only. Alternating movements were performed very slowly and clumsily with the left hand, rather better in the right hand and in both feet. Individual finger movements were very poor on the left, and slightly impaired on the right. There was marked ataxia in all limbs, particularly so on the left side. The gait was reeling, and constantly deviated towards the right. The tendon jerks were all more brisk on the left, and the left plantar response was less frankly flexor than the right. The abdominal reflexes were present and equal. Sensibility was unimpaired.

PROGRESS.—Whilst at a convalescent hospital he had an attack of pain in the right side of the face, and it was thought that there was a slight depression to pinprick over the right trigeminal area. The corneal reflexes were, however, not impaired. An electro-encephalogram on March 6, 1944, was normal. Air encephalography was not carried out. In November, 1946, he still complained of difficulty in balance and weakness of the left arm and leg.

SUMMARY OF FINDINGS.—This patient had a severe closed head injury followed by dysarthria of "cerebellar" type, hypotonia and ataxia of the limbs, particularly on the left side, and slight personality change.

Case 4.—A trooper, aged 19, was injured in a motor cycle accident on July 3, 1941. There was stupor for three days, and a post-traumatic amnesia of three weeks. No fracture was seen in radiographs of the skull. On regaining consciousness it was reported that speech was very dysarthric. On examination on Aug. 11, 1941, he

was alert and co-operative and showed no signs of intellectual impairment. Slurring dysarthria was very evident, speech being thick and lacking in definition.

CRANIAL NERVES.—The right pupil was larger than the left and reacted less well to light. When he looked downwards there was diplopia from paresis of the right superior oblique muscle. The external ocular movements were otherwise full, and there was no nystagmus. The right lower face moved less than the left in emotional and associated movements.

MOTOR FUNCTIONS.—There was probably some hypotonia of the right hand, but no weakness or ataxia. Individual and alternating movements of the fingers were not so well performed on the right as on the left, and toe wriggling was slower on the right than on the left. His gait was a little unsteady, and he was prone to veer towards the right. The tendon jerks and abdominal reflexes were all present and equal, and both plantar responses were flexor in type.

PROGRESS.—The signs persisted unchanged, and he was invalided from the Service on Feb. 11, 1942. When re-examined a year later he still had diplopia and dysarthria. The facial weakness had cleared up. He was reading for a degree at a University.

SUMMARY OF FINDINGS.—A severe closed head injury showed, as recovery occurred, dysarthria, diplopia from paresis of the right superior oblique muscle, and hypotonia of the right hand. The dysarthria and diplopia were still present eighteen months after the injury.

Case 5.—A rifleman, aged 21, was crushed between a lorry and a steel girder on Dec. 6, 1941. He had a post-traumatic amnesia of only about six hours. Radiographs showed a comminuted fracture in the anterior part of the left parietal bone. He stated that for several days after regaining consciousness he was totally unable to make any comprehensible sounds although knowing quite well the words he wished to utter. It was two weeks before he was able to make himself understood. He was able to grasp firmly, but the hands were so unsteady that he was quite unable to carry food to his mouth. On examination on Dec. 23 he was found to be alert, cheerful and rather euphoric, but with no other evidence of personality change or intellectual impairment. Dysarthria was the most striking feature, and he was very difficult to understand. The speech was slow, the tone monotonous, and the words broken up into separate syllables.

CRANIAL NERVES.—The pupils were dilated and eccentric but equal in size. The reactions to light and convergence were normal. A slight but well sustained nystagmus was present. There was neither squint nor diplopia. There was a slight left lower facial weakness, best seen in emotional and associated movements.

MOTOR FUNCTIONS.—Tone was generally diminished in all limbs, and the right hand grasp was less strong than the left. There was a slight ataxia with terminal accentuation in both upper limbs, but more on the right than on the left. In the lower limbs a slight degree of ataxia was noted in the left leg only. Alternating movements of the hands and individual movements of the fingers were impaired on both sides, but the right side was the more severely affected. The tendon jerks were all present and equal. The plantar responses were variable; on one occasion only were they frankly extensor. The gait was slightly ataxic.

PROGRESS.—An unexplained attack of fever of 103° F. lasting about two days occurred on Dec. 15, 1941. The cerebrospinal fluid was normal. Electro-encephalography on Feb. 2 1942, was normal except that the dominant frequency was seven a second.

When re-examined on Jan. 15, 1947, he had just failed in an examination for Chartered Accountancy because he could not write fast enough. His right hand was still so unsteady that he had to write with his left hand, but even this was slow. In addition to a moderate ataxia of the right upper limb there was at times a rhythmical Parkinsonian-like movement of the fingers, a tremor in which the fingers flexed with a coarse rhythm. There were other abnormal movements of the right hand of an athetotic type; for example, while writing with his left hand, the right forefinger would become hyperextended and pointing upwards from his desk in a peculiar posture which others remarked on. His speech was still ataxic, but his mental powers were well preserved.

SUMMARY OF FINDINGS.—This patient had crush injury of the head with a post-traumatic amnesia of six hours. He was subsequently anarthric for several days, and thereafter was severely dysarthric. Slight generalized hypotonia was present, together with some ataxia and loss of discrete digit movements. The gait was slightly ataxic. Both the right hand and speech were still severely affected five years after the injury.

Case 6.—A Flight-Sergeant, aged 21, sustained a closed head injury when his plane crashed on April 19, 1943. He was suspected of having a subdural hæmatoma, and four burr holes were made with completely negative findings. Further details of his condition in the early stage are lacking. There was a post-traumatic amnesia of about six weeks. On regaining consciousness he complained of inability to use any of his limbs, although they were in no way paralysed and could be moved freely. The right half of the face was immobile. There was constant diplopia and complete speechlessness. After a month the anarthria began to diminish. He himself described how he "gained one syllable a month" and how by January, 1944, he was able to "get out eight or nine words with one breath." Six weeks after the return of consciousness (in July, 1943) the right hand began to tremble as it lay on the bed. He did not think that movement of the arm increased this tremor. The tremor grew steadily worse, and in October the right leg and the head began to shake. By December the tremor was so violent that it shook his body. He was unable to control the tremor by an effort of will. It stopped during sleep.

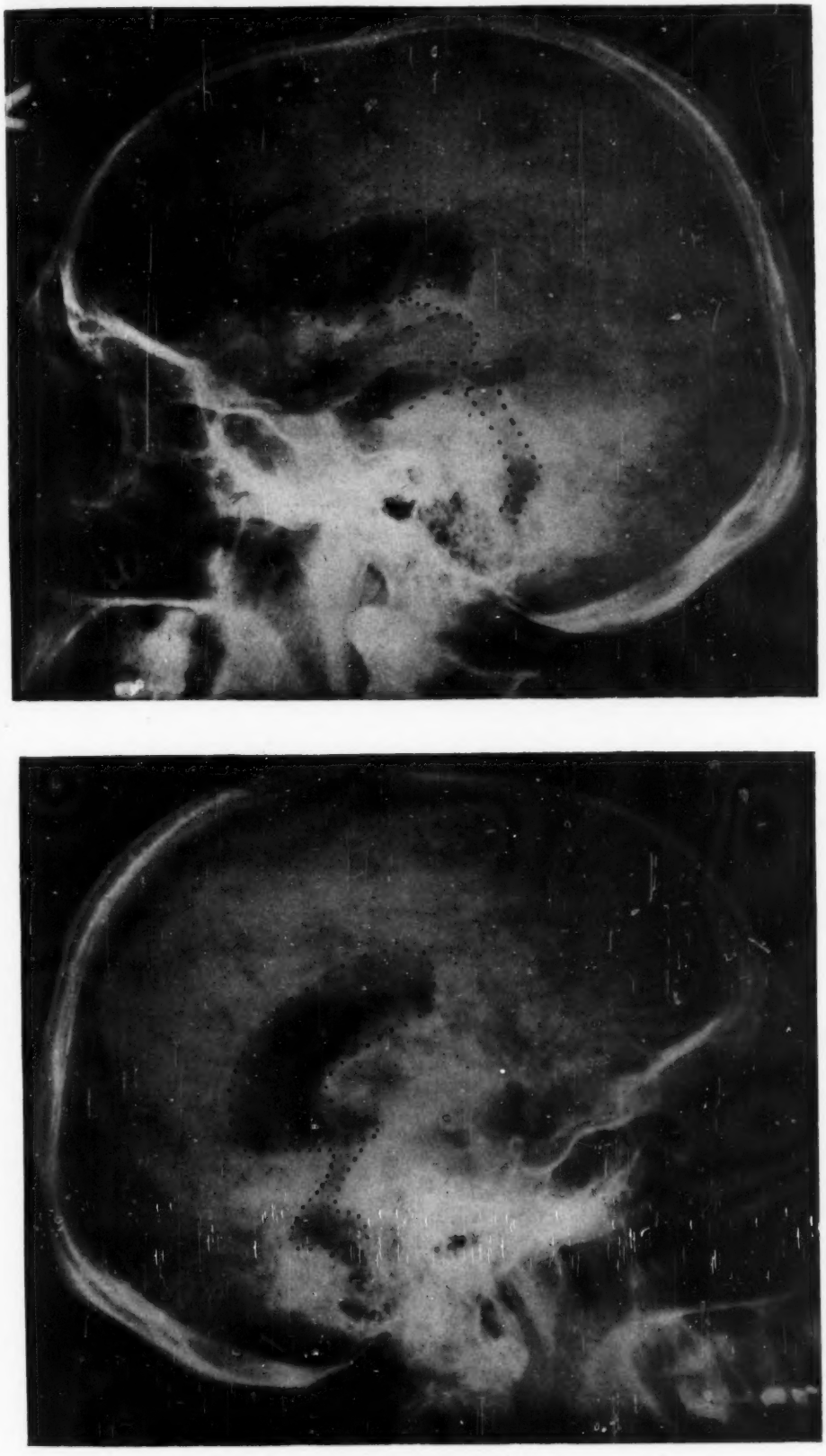
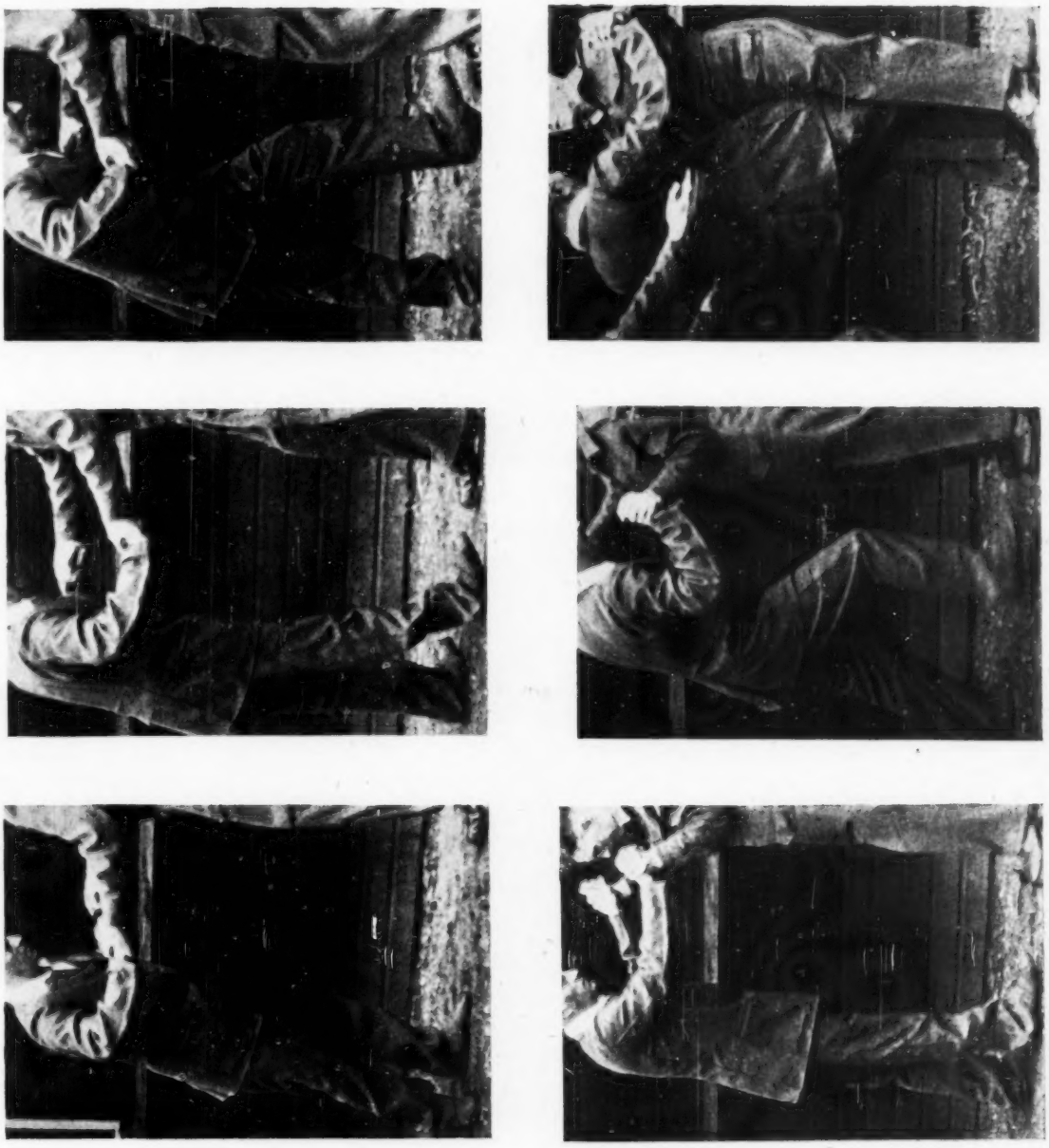


FIG. 1.—Air encephalograms in Case 1, to show dilated aqueduct. The air outline has been clarified by the dotted line. There is also a considerable quantity of air in the posterior fossa and over the occipital lobe : (*a*) brow up ; (*b*) brow down.

FIG. 2.—Extracts from a film taken of Case 1, to show lid-retraction, ataxia, abnormal movements of lips, hands, and lower limbs, and inability to maintain balance.



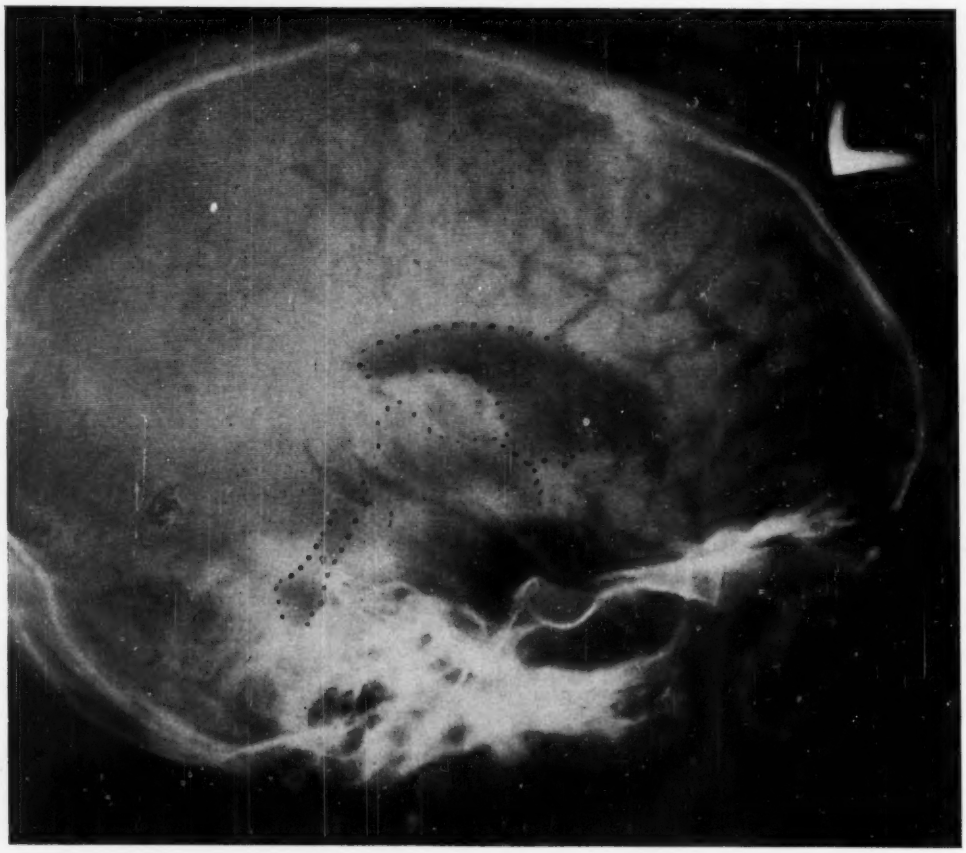


FIG. 3.—Air encephalogram in Case 2, to show dilatation of the aqueduct. The air outline has been clarified by a dotted line.

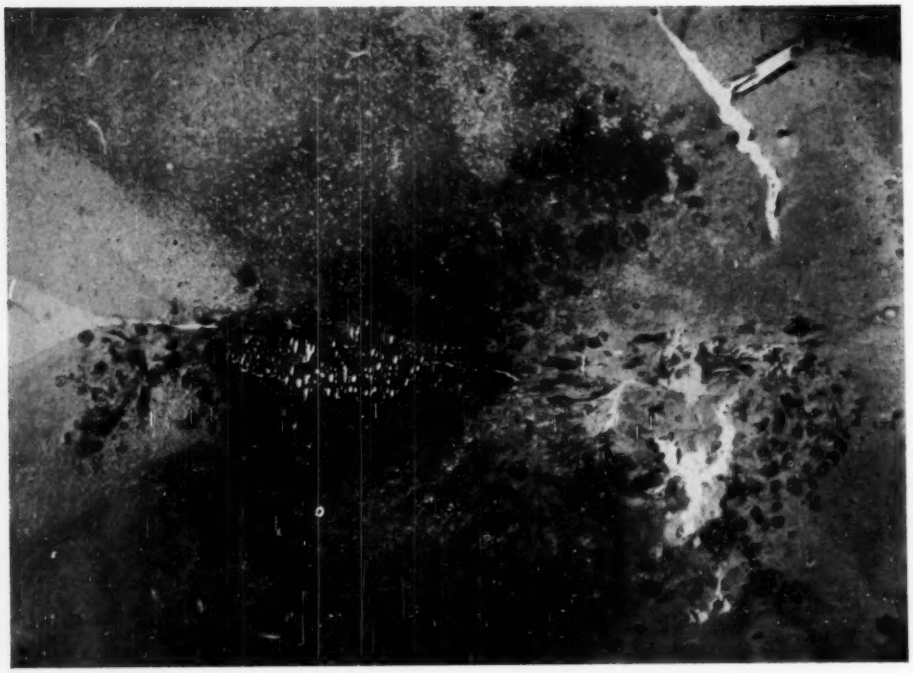


FIG. 4.—Section of the mid-brain in a case of severe head injury which survived for two days. The posterior extremity of the third ventricle is seen at the left of the section, with extensive hæmorrhages between and within the red nuclei.

On examination on Jan. 10, 1944, he was found to be euphoric but there was no evidence of intellectual impairment. Memory and grasp of current events were normal. There was severe dysarthria ; his speech was slow, monotonous, and somewhat slurred.

CRANIAL NERVES.—The right pupil was slightly larger than the left but both reacted normally to light and on convergence. There was widening of the right palpebral fissure. There was inward deviation of the right eye and slight limitation of elevation. Nystagmus was absent. Slight weakness of the right lower face and a slight and doubtful deviation of the tongue to the right were noted, but otherwise the remaining cranial nerves were normal.

MOTOR FUNCTIONS.—The right arm was the seat of a marked tremor affecting all segments. In the lower extremities the right leg showed a similar tremor but less severely so, and only the proximal part of the limb was affected. The rate was about four oscillations a second. There was a slight nodding tremor of the head, which was accentuated when he turned the head towards the right side. Tone was slightly increased in the right arm and leg, while the left limbs seemed hypotonic. Power was very slightly reduced on the right side, and voluntary movements were interrupted by a jerky and irregular ataxia, which was not, however, exaggerated terminally. He was totally unable to walk, or even to hold himself erect without support. All the tendon jerks were pathologically increased. The plantar responses were flexor. Sensory functions were normal for pinprick, light touch, and vibration, but postural sense and two-point discrimination were grossly defective in the right hand and foot.

PROGRESS.—His condition remained unchanged during his stay in hospital. Electro-encephalography gave entirely normal results. A diagnosis of traumatic lesion of the mid-brain was made, and invaliding from the Services was advised. In November, 1946, his mother wrote to say that shakiness still prevented him from walking or writing, and that the eyes were still " crossed."

SUMMARY OF FINDINGS.—This patient had a severe closed head injury with long post-traumatic amnesia. One year later there was still severe dysarthria, coarse static tremors of the head and right limbs, diplopia, sensory loss and questionable pyramidal signs on the right side, and inability to walk or even stand.

Case 7.—A marine, aged 23, fell off his cycle on May 14, 1943. He was unconscious for a few hours at most, but there was a post-traumatic amnesia of two weeks. Burr holes were made on suspicion of a subdural hæmatoma, but nothing abnormal was found. The notes stated that there was initially a left hemiplegia, but this must have been of very brief duration for on June 20, 1943, it was noted that there was only some incoordination of the right leg and defective two-point discrimination on the right hand and on both feet. When examined on July 7, 1943, he complained of slight headache and of unsteadiness of the right hand. Slight dysarthria was present. He was euphoric, and memory was defective.

CRANIAL NERVES.—The pupils were equal, but the left reacted poorly to light. The reactions on convergence were good and equal. The external ocular movements were full and without nystagmus. There was slight hypalgesia in the territory of the left infra-orbital nerve.

MOTOR FUNCTIONS.—There was no weakness. Posture was well maintained, but the right arm and leg were slightly hypotonic. There was slight ataxia in the finger-nose test on the right, and definite slowing in the pronation-supination test, and, most marked of all, in hand patting. There was a similar defect in the left arm and leg, but it was slight and insufficient to be a cause of disability to the patient. All the tendon jerks were abnormally brisk, but more so on the left side than on the right. The abdominal reflexes were diminished on the left. Both plantar responses were flexor. His gait was only slightly unsteady. There was no disturbance of sensation.

PROGRESS.—An air encephalogram showed ventricles of normal size. As his condition showed no tendency to improve, he was invalided from the services in October, 1943.

SUMMARY OF FINDINGS.—This patient had a closed head injury with post-traumatic amnesia of two weeks' duration. He had dysarthria and slight pupillary inequality. Ataxia of the right limbs (and slightly so of the left), and slight intellectual and personality deterioration were still present six months after the injury.

Case 8.—A Pilot Officer, aged 26, who was injured in a plane crash on April 12; 1942, had post-traumatic amnesia for two to three weeks. No information of the early condition was obtainable except that the reflexes were all present and the pupils equal.

When examined on April 29 he was still slightly confused. His voice was weak, and his speech dysarthric. The pupils were equal, and the reactions normal. There was diplopia from paresis of the left superior oblique muscle. There was no nystagmus. Apart from a slight left lower facial weakness the remaining cranial nerves were normal.

MOTOR FUNCTIONS.—There was, at most, questionable weakness of the right hand. The outstretched right arm drooped, and the hand tended to hyperpronate. The tone in the right arm was diminished, and there was moderate ataxia in the finger-nose test. Pronation-supination was much slower and more clumsy with the right arm than with the left. There was only a very slight ataxia of the right leg. The tendon jerks and abdominal reflexes were all present and equal, and the plantar responses flexor. There was no disturbance of sensation.

PROGRESS.—During the four months he remained in hospital most of the signs regressed, but on his discharge on Sept. 4, 1942, he still showed slight ataxia in the right

arm, and the diplopia and left lower facial weakness were still present.

SUMMARY OF FINDINGS.—This patient had severe closed head injury with subsequent dysarthria, diplopia from palsy of the left superior oblique, left lower facial weakness, and slight ataxia of the right arm and leg.

Case 9.—A Warrant Officer, aged 27, had two flying accidents. After the first, on July 7, 1941, he had post-traumatic amnesia for ten days, and after the second, on July 1, 1942, of some five minutes. Between the accidents he continued to fly but felt his "nerve" had gone, and hated flying. After the second crash his disinclination to fly increased and he became depressed. When examined on Sept. 5, 1942, his principal complaints were headache, depression, slurred speech, and trembling of the right hand. He was markedly dysarthric. The pupils were equal, but irregular in outline. The reaction to light was poor, but quite good on convergence. There was a slight irregular nystagmus on full lateral movement. The left lower face moved less than the right.

MOTOR FUNCTIONS.—Power was well maintained. There was a slight increase of tone in the right arm, with a minimal degree of ataxia in the finger-nose test, and much more slowness of discrete and alternating movements in the hand and fingers. The tendon jerks were increased on the right. The abdominal reflexes were present and equal, and both plantar responses were flexor. There was no alteration of sensibility.

PROGRESS.—No significant change occurred, and he was discharged on Sept. 29, 1942. Radiographs of the skull were normal.

SUMMARY OF FINDINGS.—This patient had fairly severe closed head injury with a second and much slighter head injury a year later. After the second injury he was found to be depressed and irritable. Organic brain damage was shown by the dysarthria, ataxia, and clumsiness of movements of the right arm, and by the increased tendon jerks on the right side.

Summary of Clinical Signs

The cases in the present series, although differing considerably from one another in minor detail and in severity, have a strong resemblance to each other.

Speech Disorders.—Dysarthria was a prominent feature of every case and, with the exception of Case 7, was severe. In four patients the early histories showed that there had been initial anarthria or mutism. In Case 1 complete anarthria persisted for three months, in Case 2 for some two weeks, and in Case 5 for several days. This last patient, who had a relatively short post-traumatic amnesia (a crushing injury) was able to recollect the early anarthria and to describe his inability to produce articulated sounds. Case 6 was able to describe the process of the return of speech. He remarked quite spontaneously that at the end of eight months he was able to "get out eight or nine words with one breath." In four of the patients the character of the dysarthria was described by observers as being typical of that associated with disease of the cerebellum or its peduncles. Where a more explicit description was given, it appears that the speech was slow, slurred, and scanning. In two patients (Cases 1 and 2), in whom return of speech was watched over several months, it was suggested that the initial mutism was due to an inability to co-ordinate breath expulsion with glottis closure and articulation. This phenomenon was also observed in two cases with gunshot wounds of the posterior fossa resulting in brain-stem and cerebellar damage. The recovery went through the stage of forced and unco-ordinated whispering before actual sounds were produced: the condition might be described as an asynergia of speech. When the voice had become strong it was high-pitched, very monotonous, and somewhat explosive; but what chiefly attracted attention was a remarkable lengthening of vowel sounds, whereby a hissing or bleating quality was imparted. It was quite unlike that ordinarily associated with cerebellar disease, for in addition to the gross ataxia there seemed to be some other motor disorder.

Ataxia.—In all the patients except Case 4, pronounced ataxia was a striking feature, and in most it was a gross and disabling symptom. Both sides of the body were severely affected in Case 1; in the others one side was chiefly or alone affected. In general it may be said that the ataxic disturbances were of the nature commonly found in severe cerebellar disease. In Cases 1 and 2, oscillations accompanying willed movements were so coarse and of such amplitude that the patient was quite unable to bring his finger to rest on a desired point. In all cases the ataxia was associated with marked inability to perform repetitive movements. When there was difficulty in performing repetitive movements, the facility with which individual movements of the digits could be executed was always impaired, but to a relatively less degree.

Loss of Balance.—Difficulty in maintaining balance and unsteadiness of gait were met with in seven of the nine patients, and in some instances the loss of balance was so extreme that walking was impossible without strong support. None of the patients complained of vertigo.

Static Tremor.—In three of our patients a coarse static tremor unassociated with willed movement and persisting for long periods was a very striking

feature. In Cases 1 and 2 the tremor was confined to one hand, but a nodding tremor of the head was often simultaneously present; in Case 6 the tremor affected both arm and leg. In no case could the tremor be stopped voluntarily, but it ceased during sleep. Although showing slight differences, the main characteristics of the tremor in these three patients were very similar. The movements, as they affected the digits, were usually of alternate flexion and extension often through a range of twenty or thirty degrees; but in Case 1 the digit movements were simultaneously associated with a supination-pronation movement of the forearm and hand. In this patient a curious feature was the way in which the tremor would shift from one part of the hand to another, at one time affecting the thumb and index, at another the ring and little fingers. In all three the tremor was coarse, and in Cases 1 and 2 the rate was between two and a half and four oscillations a second, very similar in rate to that seen in paralysis agitans. These rhythmic movements bear a considerable likeness to certain of the tremors studied by Holmes (1904) in which, from the presence of associated signs and, in two cases, from the results of post-mortem examination, a lesion in the tegmentum of the mid-brain was held to be responsible. The tremor was regarded by him as being the result of damage to the red nucleus or superior cerebellar peduncle.

Muscle Tone.—In six patients (Cases 2, 3, 4, 5, 7, 8) the resistance to passive stretching of the muscles was subnormal. In all but one of these (Case 3) the hypotonia was limited to one side, and in all it was predominant on the side showing most ataxia.

Impairment of Function of the Pyramidal Tracts.—Except in Case 4, the patients showed at some period changes in the reflexes which suggested a lesion in the pyramidal tracts. The resulting disturbances were usually slight, but they may provide a clue to the localization of the lesion. In six patients (Cases 1, 2, 3, 5, 6, 9) the reflex abnormalities were confined to, or predominated in, the side affected by ataxia and tremor. They were bilateral in one patient (Case 7); and in Case 8, where the "cerebellar" and pyramidal signs were alternate, the pyramidal signs were slight and had entirely cleared up three months after the injury. The tendency of both cerebellar and pyramidal signs to affect the same side of the body was a striking feature and suggests that the lesion lay in the mid-brain and that the cerebellar efferent pathway was damaged above its decussation in the mid-brain. For example, in Case 2 the left arm and leg showed not only loss of tone and gross ataxia, but also Parkinsonian-like tremor and increase of the tendon reflexes. It is possible that some of the alteration in reflex activity may be caused by injury to other descending motor tracts.

Loss of sensation was detected in only one case (Case 6) and affected the same side as showed both cerebellar and pyramidal signs.

Cranial Nerve Involvement.—Disturbance of cranial nerve function was inconspicuous in these cases, except that in all there was some oculo-motor abnormality. In some there was a nuclear type of oculo-motor paresis, while in others the pupils were unequal or their reactions abnormal. Ptosis and lid-retraction were also observed. In only four patients was nystagmus noted, and this was usually slight.

Discussion

Severe ataxia of the limbs and speech in itself provides a striking post-traumatic syndrome. These cases, however, show more than this, for in addition there was often a Parkinsonian-like tremor, pupillary and oculo-motor disorders, loss of balance, and pyramidal-tract signs. The association of these signs, provided they are due to one lesion, indicates a mid-brain injury. An interesting clinical feature of a unilateral mid-brain lesion at about the level of the lower part of the red nucleus is that, if the superior cerebellar peduncle (after decussation) and the crus are damaged, the expected result would be both cerebellar and pyramidal-tract signs in the contra-lateral limbs. In addition there might be Parkinsonian-like tremor from injury to the red nucleus and substantia nigra, while sign of involvement of the oculo-motor nucleus and medial fillet might easily occur. All these clinical features were well seen in this group of cases, especially where the signs were chiefly unilateral with the cerebellar and pyramidal signs affecting the limbs of one side. The clinical signs alone, therefore, provide strong evidence of mid-brain injury, while the remarkable dilatation of the aqueduct of Sylvius seen in two cases strongly supports this view.

Hæmorrhagic lesions of the mid-brain are well-known in autopsy studies of rapidly fatal cases. Fig. 4 (kindly lent by Lt.-Colonel Schorstein, R.A.M.C.) illustrates such a lesion from a patient who died about two days after a severe head injury. Holbourn's (1943) convincing studies of the mechanism of brain injury did not include the brain stem. Courville (1945) suggests that mid-brain injury is produced mechanically by bruising against the tentorium, or a rotational strain of the hemispheres pulling on the brain stem. Case No. 5, however, was a crushing injury, in which Holbourn's shearing injury due to rotation could not play a part. In

this case the skull distortion from compression might have led to some squeezing effect of the brain towards the tentorial opening, with resulting mid-brain damage. It might be thought that hyperpyrexia (Freeman and Dumoff 1944) might lead to damage causative of these striking signs, and in Case 1 there was high fever. In hyperpyrexia, however, the motor dysfunction is symmetrical and purely cerebellar. There is also evidence that cerebral anoxia from respiratory arrest may rarely play an important part in brain damage after head injury, but in anoxia the cerebral hemispheres are first affected.

Summary

Nine cases of severe closed head injury with severe signs of mid-brain injury are reported. The dominant clinical signs were cerebellar, and included severe dysarthria and disturbance of balance. The cerebellar signs were usually most pronounced on one side, and the limbs of the side showing the maximum ataxia tended also to have increased tendon reflexes, Parkinsonian-like tremor, and, in one case, sensory loss suggesting injury to the medial fillet. These signs are thought to indicate injury to the mid-brain above the decussation of the superior cerebellar peduncles. Additional signs of mid-brain damage were oculo-motor and pupillary disturbances. In at least one case there was early rigidity of all four limbs.

In two cases air encephalography disclosed a marked dilatation of the aqueduct of Sylvius.

We are indebted to Sir Charles P. Symonds, K.B.E., C.B., M.D., F.R.C.P., for his interest and help, and to a number of medical officers at the Military Hospital for Head Injuries, Oxford, for their careful notes. The Director-General, Army Medical Services, has given permission for publication. The Medical Research Council supplied secretarial help.

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A CLINICO-PATHOLOGICAL REPORT ON UNUSUAL CASES OF CHRONIC ENCEPHALITIS

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THE purpose of this paper is to describe three unusual cases of encephalitis which do not fit easily into the recognized types. They have in common an insidious onset, a subacute or chronic course, and a rather diffuse spread of the lesions throughout grey and white matter. It is not suggested that these common features necessarily imply any ætiological relationship between the cases, each of which has its own clinico-pathological profile.

Case Histories

CASE 1

A girl, aged 6 years, was admitted to the Leavesden Hospital, Hertfordshire, on Feb. 21, 1940 and died on July 2, 1940.

HISTORY BEFORE ADMISSION.—The child was thought to be perfectly well on Sept. 1, 1939, when she was evacuated from London because of the expected bombing. A month thereafter (five months before admission to hospital) she became lost in the streets and later seemed to have no recollection of having been lost. When her mother visited her a week later the child appeared not to recognize her. She was noted to be " difficult to handle " in school, and at the request of the teacher was removed. About December it was noted that she could not hold things in her hands. Seven weeks before admission she started falling frequently, first to the left, then forward. This grew progressively worse until at the time of admission she could hardly walk two or three steps without falling. Apparently her mental condition had deteriorated steadily, since at the time of admission she did not seem to recognize her parents and could not feed herself.

The family and past histories were irrelevant.

EXAMINATION.—The patient lay quietly in bed propped on pillows, head dropped on the left shoulder, arms flexed over the chest. She was pale and thin, whined when touched, and tended to bite at anything placed near her mouth. Her temperature was 100° F. General physical examination revealed no other positive findings. Neurological examination showed that the pupils were dilated and equal, and reacted normally to light. There was slight blurring of the nasal side of the discs. The eyes deviated to the left, but voluntary movements were normal. No other cranial nerve abnormalities were noted. There was no definite weakness of the arms or legs. There was thought to be increased tonus in the legs. The deep reflexes were equal and active. The abdominal reflexes were present in the upper quadrants but not in the lower.

Laboratory studies revealed that the urine was normal; there were 5·1 million red blood cells per c.mm. of blood; the hæmoglobin was 84%; and the white blood count was 7,600, with 73% neutrophils, 24% lymphocytes, 2% monocytes, 1% eosinophils.

Cerebrospinal fluid obtained from the ventricles on Feb. 17 contained one cell per c.mm. Cultures were negative. The fluid was anticomplementary.

COURSE.—The patient went slowly but steadily down hill. For the most part her temperature was between 98° and 100° F.; but on two occasions, each lasting three or four days, it rose daily to 102° F. After Feb. 24 the abdominal reflexes were absent. Marked tremor of the arms was noted on Feb. 26. On that date the ankle jerks were absent and the plantar responses normal. On Feb. 28 there was an increase in tonus of the legs. The child had not been heard to speak at all, and she exhibited very little voluntary movement. Her breathing was shallow and accompanied by moans. There was an occasional sudden jerk, in which the eyes turned upwards. On March 12 she was still fretful, and still exhibited the biting reflex. Cardiac irregularities were noted on June 26, and she died on July 2, about nine months after the onset of her illness.

NECROPSY EXAMINATION.—Except for pulmonary congestion, the significant findings were restricted to the central nervous system. The brain weighed 1,220 g. The pia-arachnoid was intensely congested. When the brain was sectioned, the grey matter was thought to be pinker than usual, and there was an increase in the size and number of the visible cerebral vessels.

MICROSCOPIC FINDINGS.—Perivascular infiltration by lymphocytes and plasma cells was found in almost all regions of the brain. It was relatively slight in the

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meninges, which were slightly fibrosed, but conspicuous in the cerebral cortex. All cortical regions were affected, but the frontal more heavily than any other. The infiltration consisted of mainly lymphocytes around the larger vessels, and predominantly plasma cells around the precapillaries and capillaries. In this respect the histological picture resembled that commonly seen in general paresis (Fig. 1). The iron reaction was, however, negative throughout the brain, and no spirochætes were found. There was undoubtedly some diffuse loss of nerve cells in all cortical areas, particularly evident in the frontal lobe, but its degree was difficult to assess since the cyto-architecture, especially in the deeper layers, was often obscured by an increase of cellularity due to a proliferation of the microglia and macroglia in addition to the inflammatory cells described above. The proliferation of microglia was both diffuse and focal, the latter giving rise to glial nodules, which were found not only in the cortex but also in most other parts of the grey and white matter of the brain. These glial nodules were independent of the blood vessels but occasionally formed around degenerating nerve cells. The majority of nerve cells showed changes best described as Nissl's acute cell change, though in some the change was more severe, to the point of dissolution of nuclei and ghost-cell formation. No inclusion bodies were seen in cells of the cortex or elsewhere. A moderately increased amount of fat was present in the nerve cells as well as in the endothelial cells and adventitial histiocytes of many medium-sized blood vessels. Holzer preparations showed an increase of glial fibres, particularly in the marginal and deepest layers of the cortex.

Similar changes were found in the corpus striatum and the thalamus, while the globus pallidus was largely spared. Damage to the substantia nigra was fairly heavy, approaching in extent that often seen in chronic encephalitis. It appeared to be shrunken, and Holzer preparations showed moderately heavy astrocytic proliferation. The number of its nerve cells was reduced, and many of the remaining cells showed various stages of severe degeneration, having shed their melanin pigment which was to be seen in hyperplastic microglial and adventitial cells in the vicinity. The inflammatory changes and microglial nodules were not conspicuous in the substantia nigra, but were found to an appreciable degree elsewhere in the midbrain and in the pons. They were mild in the medulla and cerebellum. The spinal cord showed no inflammatory changes, but there was some demyelination and increase of glia in the pyramidal tracts thought to be secondary to the cerebral changes.

A noteworthy feature of the case was the widespread diffuse glial proliferation throughout the cerebral white matter. For the most part this glial fibrosis was associated with very little alteration in the myelin or in the axis cylinders (Fig. 4), but in the centrum semi-ovale and the internal capsule it was associated with patchy demyelination. The demyelinated areas (Fig. 2) were irregular in outline, often poorly demarcated from the surrounding tissue, and shown by Nissl's stain to be cellular astrocytic scars (Fig. 3). In these areas the perivascular infiltration was most intense, and isolated plasma cells were noted in the parenchyma. The axis cylinders were reduced in number and were irregularly swollen and vacuolated and frequently fragmented. Glial fibrosis without demyelination was distributed in a patchy fashion throughout the brain stem, especially in perivascular areas and in the region of the olives and the nuclei of the pons.

Discussion of Case 1

The finding meriting special emphasis is the widespread sclerosis of the white matter, revealed most characteristically in the sections stained by Holzer's technique and associated with irregular patches of demyelination in the most densely involved areas. Patches of demyelination have been found frequently as pathological residuals of an encephalitic process, and the German literature contains several reports of cases in which the demyelinated patches were thought to be indistinguishable from the plaques of multiple sclerosis* (Kufs, 1923; Bill, 1922; Peters, 1935). In our case the demyelinated areas were too irregular in outline and too poorly demarcated from the surrounding tissue to be taken for typical multiple sclerosis lesions. Globus (1937) has reported a case of encephalitis having an acute onset, running a course of three years, and developing such extensive scar formation in the midbrain as to cause clinical symptoms simulating brain tumour.

The cases in the literature most closely resembling ours are those reported by Scholz (1923), Bodechtel and Guttman (1932) (two cases), and van Bogært (1945) (three cases). In all these patients the illness developed gradually, five of the six patients were children, and in all the illness ran a sub-acute or chronic course. In all the pathological findings were mild meningitis and widespread perivascular lymphocytic and plasma-cell infiltration, microglial nodule formation, and widespread fibrous gliosis of the white matter. Scholz considers his case to be one of chronic epidemic encephalitis. Bodechtel and Guttman, and van Bogært, attach considerable importance to the finding of sclerosis of the white matter. On the basis of the changes in the white matter, Bodechtel and Guttman dismiss the diagnosis of encephalitis and classify their cases as diffuse sclerosis. Van Bogært specifically separates his cases from the primary demyelinating diseases, favours the possibility that they may be cases of encephalitis, and classifies them as "sub-acute sclerosing leuco-encephalitis." Van Bogært's stand in this matter seems entirely reasonable and only has the shortcoming, which he mentions

* It remains to be seen to what degree this problem will be influenced by the recent claim of Margulis and others (1946) to have identified the same virus in postvaccinal encephalitis and disseminated sclerosis.

himself, that a new term having only morphological significance is introduced (or rather, an old term employed by Spielmeyer but given a somewhat more precise meaning). It seems to the present writer that nothing is gained by classifying such cases as these with the demyelinating diseases. Whatever the final ætiological classification may prove to be, the present case confirms the reality of van Bogært's clinico-pathological concept.

Unfortunately, the serological studies of the spinal fluid are not complete, but neither the clinical course of the illness nor the pathological findings suggest a diagnosis of paresis.

Case 2

A man, aged 30 years, was admitted to Cane Hill Hospital, Coulsdon, Surrey, on Oct. 16, 1941, and died on Jan. 5, 1945.

History Before Admission.—Since this patient's illness was discovered shortly after he had enlisted in the Army, the question of compensation and service-connected disability arose, so that the history prior to June, 1940, may be inaccurate. He stated that he was well until 1930, when he had some febrile illness with drowsiness. Thereafter he had attacks of double vision and impaired usefulness of his left leg. His wife insisted that he was entirely well until he joined the Army.

He was conscripted in June, 1940, and was discharged as medically unfit in December, 1940. During this time he complained of headaches, attacks of double vision and blindness, and of drowsiness. Under observation before discharge from the Service, he was described as rather childish and euphoric. He was dirty in his habits, boastful, and a pilferer. He had marked dysarthia. His pupils were small, equal, and slightly irregular, and they reacted sluggishly to light. The abdominal reflexes were absent. There was weakness of the left leg, and the left knee jerk was hyperactive. The plantar responses were normal. There was some inco-ordination in the heel-to-knee test. Slight coarse nystagmus and diplopia occurred on looking to the left. Spinal puncture revealed 8 cells per c.mm., a negative Wassermann reaction, 50 mg. of protein per 100 c.cm., and a normal colloidal gold curve. The diagnosis at the time of discharge from the Service was "post-encephalitic syndrome."

From Dec. 31, 1940, until Oct. 16, 1941, he lived at home. He occasionally committed senseless and ill-planned thefts, such as riding away on another person's motor-bike.

History After Admission.—At the time of admission to Cane Hill Hospital he was described as euphoric and poor in judgement. He regarded his ill-health as a joke. He had a poor memory, had difficulty in performing simple arithmetic, and expressed the grandiose idea that he was a personal friend of Sir Archibald Sinclair. His speech was slow and deliberate. He was slightly ataxic and was clumsy in the use of his fingers.

The Wassermann reactions of the blood and spinal fluid were negative. The spinal fluid protein was 80 mg. per 100 c.cm. The colloidal gold curve was 0122210000. Spinal fluid examination repeated in November, 1942, and in January, 1944, showed the Wassermann reaction negative both times. In 1942 there were 8 cells per c.mm., the total protein was 80 mg.%, and the gold curve was 1122321100. In 1944 the cell count was 7, and the total protein 50 mg.%.

In the three years following his admission to the hospital, the patient's symptoms progressed very slowly. He remained euphoric and hoarded all manner of rubbish. In November, 1942, his general physical condition was good and very little change in his neurological status was noted except that his gait was now definitely ataxic. There was slight inco-ordination in the finger-to-nose test on the left, and the plantar responses were extensor on both sides. By November, 1943, he had a spastic gait and had lost sphincter control. On Jan. 3, 1945, he was found in a state of stupor, unable to walk or talk. His temperature was 98·6° F. During the next two days he had a few epileptiform fits. He died on Jan. 5 without having regained consciousness. The final clinical diagnosis was disseminated sclerosis.

Necropsy Examination.—Significant necropsy findings were restricted to the brain. The spinal cord was not available for examination. The brain weighed 1,410 g. Both lateral ventricles, the third ventricle, and the optic recess were enlarged; the aqueduct and the fourth ventricle were normal; the corpus striatum had a brownish colour; the substantia nigra was macroscopically normal in appearance.

Microscopic Findings.—Many of the findings were identical with those in Case 1. There were, however, some significant differences.

The leptomeninges, throughout, were diffusely infiltrated with lymphocytes and plasma cells (Fig. 5), most intensely at the base of the brain in the region of the hypothalamus and optic chiasma. In the brain itself the perivascular lymphocytic and plasma cell infiltration was ubiquitous and heavy. In order of intensity, the hypothalamus (Fig. 6) and brain-stem came first, followed by the basal ganglia and then the cerebral cortex. The hippocampal region was very heavily involved, except in Ammon's horn, which was relatively lightly affected. There was also inflammatory change in the substantia nigra, but not more than in any other sub-cortical centre and without any appreciable degree of degeneration or loss of the melanin-containing pigment cells.

The inflammatory process was not confined to the grey matter, but occurred to an approximately equal degree in the white.

Microglial and macroglial proliferation was widespread. Glial nodules made up of microglial cells and astrocytes (Fig. 8) were encountered everywhere. In the centre of the nodules, nuclear debris derived from degenerating nerve cells was encountered often. Diffuse microglial and macroglial proliferation was ubiquitous, but occurred with particular intensity in the hypothalamus, chiasma and optic tract, corpora quadrigemina, the most medial portion of the cerebral peduncles, and the vicinity of the inferior olives. These areas of marked increase in cellularity were associated

with intense vascular engorgement, small hæmorrhages, and severe nerve cell changes. The number of blood vessels was especially increased in the hypothalamus, optic chiasma (Fig. 7), and the medial and inferior portions of the temporal lobe. The adventitia of the walls of many of the vessels was proliferated, and the media had a hyaline appearance.

A less intense diffuse gliosis, demonstrable in silver carbonate and Holzer preparations, was found in the marginal layer of the cortex, areas around the ventricles, the subcortical white matter, and the corpus callosum. The gliosis in the cerebral white matter was not comparable in intensity with that described in the previous case.

In all sections examined, degenerative nerve cell changes were encountered. In the cortex this was most marked in the deeper layers. Nowhere, however, was the cortical architecture very markedly distorted. Nerve cell degeneration was most intense where the inflammatory changes were marked, but was also prominent in the dentate nuclei and the Purkinje cell layer, although the inflammatory changes in the cerebellum in general were mild. Many of the diseased nerve cells were shrunken and pyknotic and had tortuous processes. Others stained very poorly and were vacuolated, and there were small foci where nerve cells had dropped out altogether or were represented only by shadow cells. Fat stains revealed excessive neutral fat droplets in the majority of the nerve cells and in the walls of many of the medium-sized vessels.

The iron reaction was strongly positive in most of the sections examined, especially in sections from the cortex and hypothalamus. Iron was found in the walls of many of the small and medium-sized vessels and in microglial cells in the neighbourhood of such vessels (Fig. 9). No spirochætes were discovered.

Demyelination was encountered only in the hypothalamus and optic chiasma, where the inflammatory changes were most severe. The demyelination was slight in comparison with the severity of the inflammatory reaction and gliosis, and occurred in poorly demarcated, small patches.

Discussion of Case 2

From the clinical and laboratory findings the diagnosis of disseminated sclerosis would appear to have been a logical one, but the pathological findings reveal no evidence for it whatsoever. The findings are almost exclusively inflammatory, and it does not seem reasonable to entertain any diagnostic possibility other than some form of encephalitis. General paresis must naturally be considered first because of the course of the illness and the positive iron reaction in many of the cerebral blood vessels. Examination of the spinal fluid on four different occasions over a period of four years always revealed the Wassermann reaction to be negative. The colloidal gold curve, which early in the illness was normal, in the course of time gradually assumed a low mid-zone character, but was never typical of paresis. Consistently negative serological findings such as these are almost never encountered in untreated paresis (Stokes, 1944). Although the iron reaction is very highly characteristic of paresis it has been described in other forms of encephalitis and therefore cannot be considered specific to paresis. Von Economo (1920) and Scholz (1923) mention pigment of hematogenous origin in the glia cells and vessel walls of their cases of sub-chronic epidemic encephalitis, and Kingo (1934, 1935) and Uchiyama (1925) noted that positive iron reactions occurred during and after Japanese B. type of encephalitis. In our case, also, the distribution of the inflammatory process was not typical of paresis, in that the hypothalamus, brain stem, and optic nerve were more intensely involved than the cortex, and that everywhere the white matter was involved almost as much as the grey. For these reasons it is felt that paresis can be ruled out.

There is no pathological evidence of a tuberculous process. The most reasonable diagnosis from the pathological point of view would, therefore, appear to be one of the forms of virus encephalitis.

It is of interest that definite evidence of acute and subacute or chronic lesions is to be found side by side in the same areas, just as in many of the examples of chronic encephalitis described in the literature. Thus, in the hypothalamus and the optic chiasma marked increase in vascularity with proliferation of the adventitia of the vessel walls and intense fibrous gliosis were noted in the same microscopic field as very recent hæmorrhages.

Case 3

A boy, aged nine years, was admitted to the Crichton Royal Hospital, Dumfries, on Nov. 12, 1943, and died on Jan. 23, 1944.

History Before Admission.—In September, 1943, it was noted that the patient showed slight lapses of consciousness His head would fall on to his chest, his hands would open once or twice, and for a second or two he would appear to be completely unconscious. He would then carry on with what he had been doing, but with a good deal of mental confusion. He would also wake up suddenly in the night, blink vigorously, and, when questioned, appear to be in a state of altered consciousness. In the daytime he would occasionally fall to the floor in such an attack. From September, 1943, he became uncertain in his gait, staggering from side to side but more often to the left, and he seemed to limp with his left foot.

In the next few weeks he became increasingly confused, so that he could not be sent on the simplest errands and on occasion did not know the whereabouts of his home or of his own room. During October he became

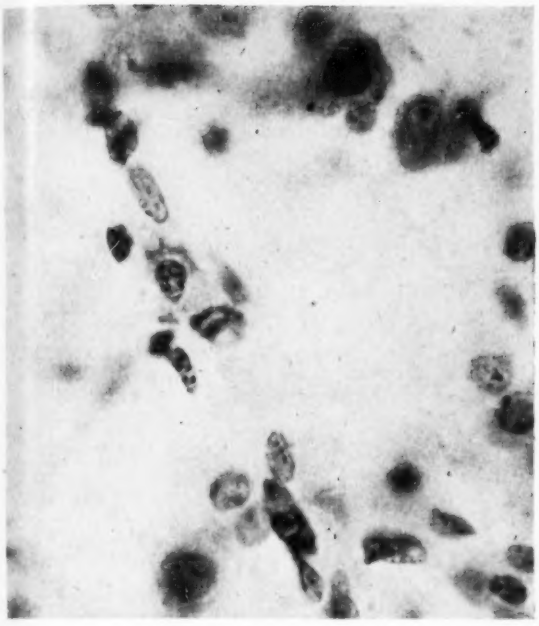
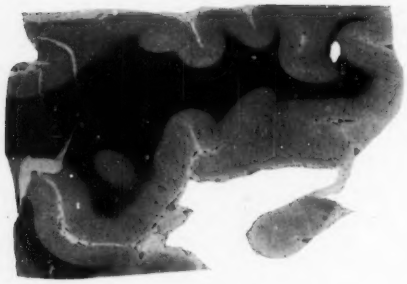


FIG. 1.—Case 1. Plasma cells around a small vessel in the frontal cortex. Nissl stain, × 850.

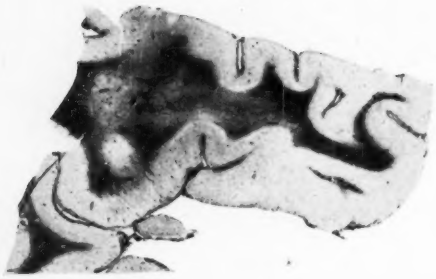
FIG. 2 (above).—Case 1. Poorly demarcated area of demyelination in the internal capsule. Heidenhain stain for myelin, × 6.

FIG. 3—Case 1. Nissl stain, higher magnification of demyelinated area shown in Fig. 2. Marked increase in cellularity and perivascular infiltration, × 27.



a)

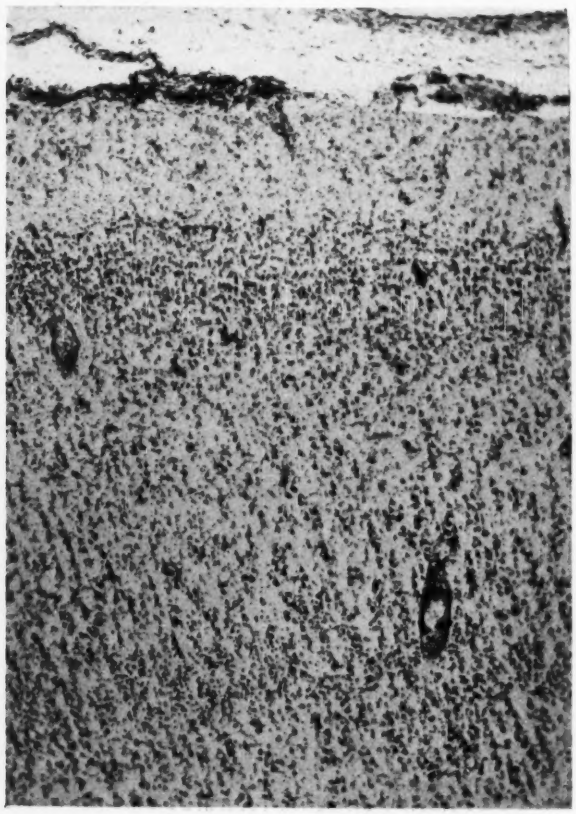
FIG. 4 (top left).—Case 1. (*a*) Heidenhain stain for myelin. (*b*) Holzer stain, showing glial fibrosis of the white matter with little demyelination, × 1·4.

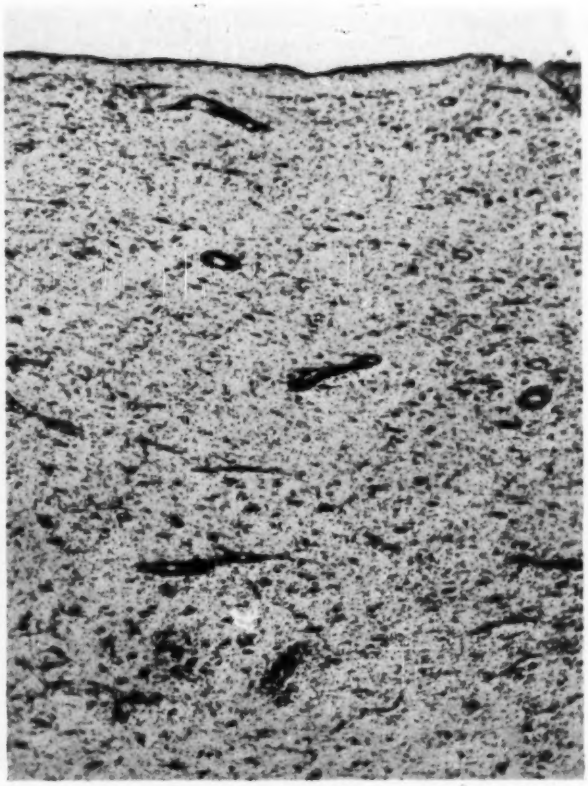


(b)

FIG. 5 (lower left).—Case 2. Meningitis, increased cellularity of cortex, and infiltration around small blood vessels. Nissl stain, × 60

FIG. 6 (lower right).—Case 2. Marked increase in cellularity and perivascular infiltration in the hypothalamus. Nissl stain, × 60.





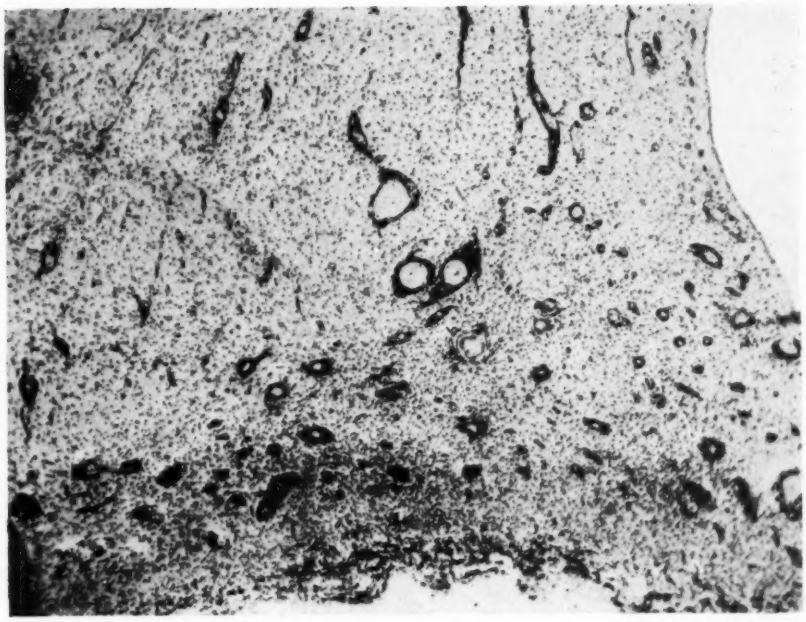


FIG. 7.—Case 2. Increased vascularity, increased cellularity, and perivascular infiltration in the optic chiasma. Nissl stain, × 55.

FIG. 8.—Case 2. Microglial nodule in the hypothalamus. Nissl stain, × 50.

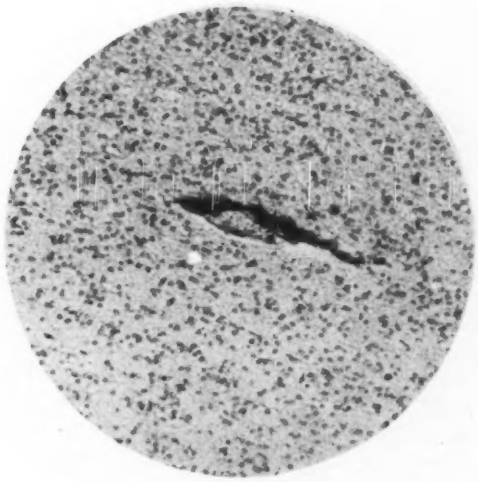
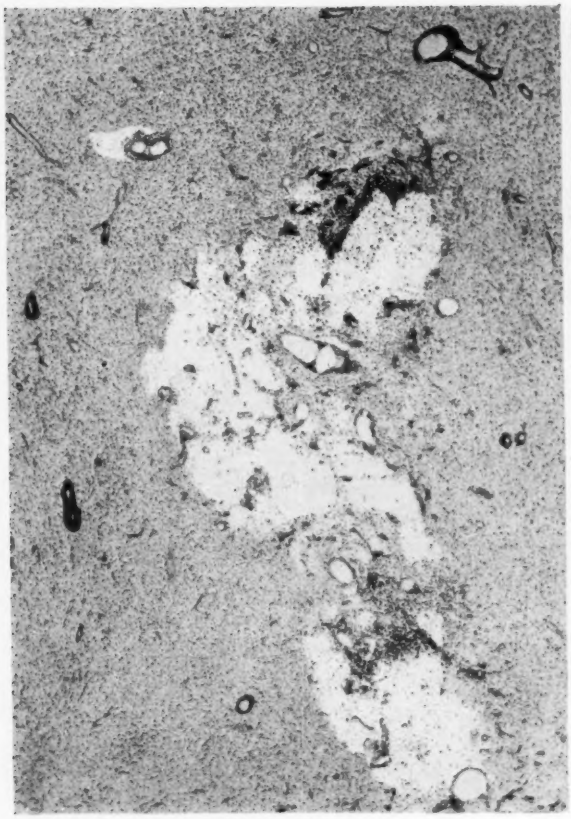
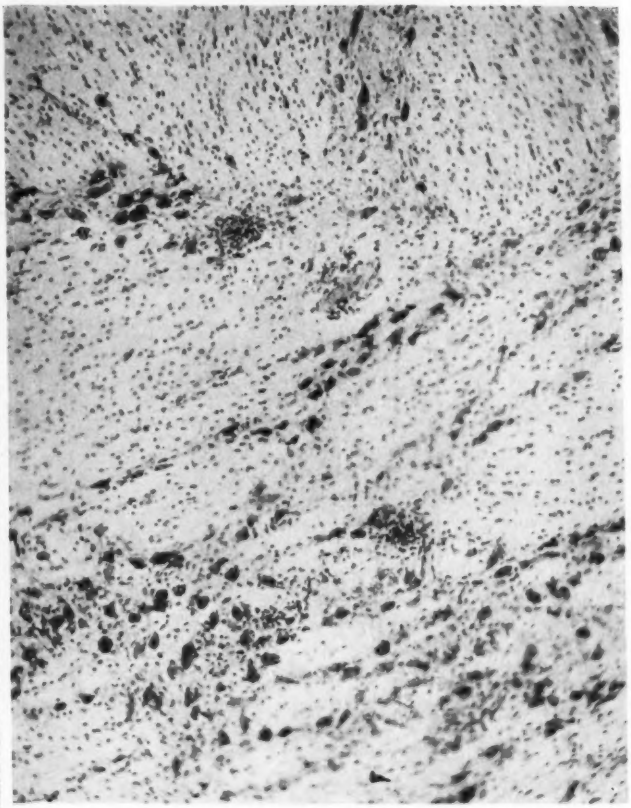


FIG. 9.—Case 2. Deposits of iron in the adventitial cells of the wall of a small vessel in the cerebrum. Turnbull's iron reaction, × 50.





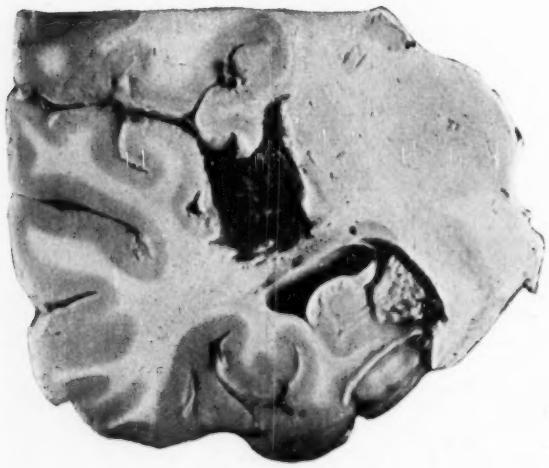


FIG. 10 (lower left).—Case 3. Area of hæmorrhagic softening in the left insular region.

FIG. 11 (top left).—Case 3. The same as Fig. 10. Area of softening showing cellular infiltration around the nearby vessels. Nissl stain, × 25.

FIG. 12 (top right).—Case 3. Glial nodules in the pons. Nissl stain, × 90.

incontinent of urine, especially at night, and later became incontinent of fæces as well. He had been losing weight rapidly before admission to hospital.

The family and past histories were essentially irrelevant except that the patient had had asthma since the age of one year, not severe enough to keep him from school. One month before the onset of his present illness he had a particularly severe attack of asthma lasting several days.

EXAMINATION.—The patient exhibited a meaningless grin and his attention was difficult to maintain. There was poverty of spontaneous speech. The optic discs were normal but there was a pigmented patch in the left fundus. The pupils and ocular movements were normal. There was slight right facial weakness. Both arms displayed tremor on activity, and the left one also when at rest. Tonus was greater in the left arm than in the right. The right foot dragged in walking. The Babinski sign was positive on the right, but there was no significant difference in tendon reflexes on the two sides. The abdominal reflexes were normal. Marked apraxia in purposeful movements was observed.

LABORATORY STUDIES.—The Wassermann reactions of the blood and spinal fluid were negative. The spinal fluid pressure was 200 mm. of water, there were three lymphocytes per c.mm., the chlorides were 750 mg.% and the total protein 45 mg.%. The colloidal gold curve was 5543210000. These spinal fluid findings were confirmed by subsequent examination. Guinea-pig inoculation with spinal fluid failed to reveal evidence of tuberculosis.

Electro-encephalography showed widespread dysrhythmia, with delta waves and short bursts of fast waves. An air encephalogram was negative. Biopsy from the left frontal region failed to support the possibility of a diagnosis of toxoplasmic encephalitis.

COURSE.—The patient went steadily downhill and died on Jan. 23, 1944.

NECROPSY EXAMINATION.—The significant necropsy findings were restricted to the brain. The spinal cord was not available for examination. The brain was markedly congested. There was moderate symmetrical enlargement of all the ventricles. A hæmmorhagic area the size of a bean was noted in the left insular region destroying part of the insula, claustrum, and putamen (Fig. 10). A few smaller areas of the same type were seen near the meninges in the occipital area.

Microscopically the lesions included small areas of cyst formation and necrosis, cellular infiltration in the meninges and around the blood vessels of the parenchyma, diffuse and focal glial hyperplasia, and extensive nerve cell degeneration.

The hæmorrhagic areas involving the insular and occipital regions were found to be areas of necrosis with cyst formation (Fig. 11). The cysts were filled with pigment-laden compound granular corpuscles and surrounded by a dense ring of astrocytic proliferation. In short, these areas had the appearance of hæmorrhagic infarcts. In the areas around the cysts inflammatory changes were very marked. There was intense infiltration of the blood vessel walls and perivascular spaces with lymphocytes and plasma cells. Myelin and Bielschowsky stains revealed the myelin sheaths and axis cylinders to have undergone extensive degeneration in these areas and to be largely replaced by glial fibres.

Although the occurrence of these cysts was limited to two areas in the cerebrum, the inflammatory changes were found in all sections examined. Thus there was a diffuse, mild lymphocytic and plasma cell meningitis. In the substance of the brain perivascular exudation of these cell types was widespread and included the smallest vessels, the walls of which were frequently plastered with plasma cells. Tiny microglial nodules were numerous throughout the cerebral cortex, basal ganglia, and brain stem (Fig. 12). These glial nodules frequently occurred around blood vessels and often contained a few plasma cells. The grey and white matter both contained these nodules and were about equally involved in the perivascular infiltration.

Except for the regions in the neighbourhood of the cysts described above, extensive demyelination was not encountered. There was some demyelination around a few of the small blood vessels in the white matter, and in these areas there was also slight microglial proliferation. The white matter everywhere had a vacuolated appearance thought to be due to œdema. Ependymal granulations were noted in the aqueduct.

In general the lesions were less severe below the thalamus than above, and the striatum was involved less than the thalamus. The hypothalamus was extensively affected. The cerebellum was involved least of all, except for the region of the dentate nucleus which manifested all the inflammatory changes described. Outside the cystic areas in the cerebrum degenerative nerve cell changes mostly of the acute type were rather uniformly distributed and were encountered at all levels. Inclusion bodies were not found. The iron reaction was negative throughout. Spirochætes were not discovered.

DISCUSSION OF CASE 3

The most interesting feature of this case from the pathological standpoint was the occurrence of the hæmorrhagic areas, having the appearance of infarcts, in the cerebrum. Von Economo specifically states that such lesions do not occur in epidemic encephalitis. He believed that the infection involved the nerve cells primarily, and that individual nerve cells frequently underwent necrosis but that large necrotic areas did not occur. He considered the glial proliferation and perivascular infiltration to be secondary to the primary disease process, viz., nerve cell degeneration. On the other hand, microscopic areas of necrosis have been described as characteristic of the acute stage of the western equine variety of encephalitis (Noran and Baker, 1943, 1944, 1945; Weil and Breslich, 1942), the eastern equine variety (Wesselhœft and others, 1938; Farber and others, 1940), the St. Louis type (Weil, 1934), the Japanese type (Uchiyama, 1925),

and of encephalitis complicating herpes (Hassin and Rabens, 1944). Noran and Baker have described the pathological changes in one case of subacute (10 weeks' duration) encephalitis of the western equine type (1945), and in three cases dying years after the onset of the illness (1943, 1944, 1945). In all these cases hypertrophic vascular lesions with narrowing and occlusion of the lumen and extensive replacement of the brain by cyst formation was encountered. They believe that in the western equine variety of encephalitis the virus attacks the blood vessels primarily, and that the other findings are secondary to the vascular lesions. In our case there were no severe lesions of the blood vessels other than the perivascular infiltrations.

In considering the resemblance of the lesions in this case to some of the extra-European types of epidemic encephalitis, it is of interest to note that none of the latter has ever been identified in Great Britain, and that so far as is known the encephalitis of von Economo is the only epidemic type that has occurred here (Brain and others, 1943 ; Editorial in the *British Medical Journal*, 1946).

The case in the literature most closely resembling our Case 3 is one described by Levy (1937). His patient was a child of 10, whose illness had its onset with convulsions, and a duration of seven months. There were grossly visible hæmorrhagic lesions which microscopically were large areas of severe necrosis. At the margin of these necrotic areas and in the macroscopically normal regions there was extensive infiltration of the vessel walls and adventitial spaces with lymphocytes ; there was diffuse glial proliferation, and a mild meningitis. Because of the lymphocytic infiltration of the vessel walls and the apparently vascular nature of the gross lesions, Levy considered his case to be a type of angiitis. He noted that veins and arteries were about equally involved and that outside the necrotic areas there was neither necrosis of the vessel walls nor serious encroachment on the lumen. It is possible that the necrotic lesions in Levy's case as well as in ours represent a stage in the development of the cystic lesions shown by Noran and Baker to be characteristic of chronic Western equine encephalitis.

General Comment

Several points requiring special emphasis are raised by these three cases. The first concerns the question of the persistence of the virus of encephalitis in the central nervous system in an active form for long periods of time. Von Economo (1920, 1931) was convinced that this occurs, but the idea is by no means generally accepted (see discussion by Stevenson, 1942). According to von Economo's conception of epidemic encephalitis, in the majority of cases the virus is eliminated from the nervous system within a few weeks (possibly leaving a permanent sequel as a result of irreversible tissue damage), but in other cases the virus remains active and the infection runs an intermittent chronic course of a duration varying from months to years. He classified his cases clinically as acute cases with protracted convalescence, sub-chronic and chronic. He used the term ' chronic encephalitis ' to designate the well-known syndromes now more commonly referred to as post-encephalitic paralysis agitans, personality disorders of a psychopathic type, and the like. His opinion that the virus frequently remains active was based on the slow development and frequently progressive nature of these disorders as well as the finding (subsequently noted by many investigators) of active inflammatory and degenerative changes at autopsy on some of these patients years after the onset of the acute illness (Meggendorfer, 1922 ; Hassin and Rotman, 1923 ; McKinley, 1923 ; Hohman, 1925, Bahr, 1935). In this respect the findings in our case support von Economo's views, but naturally a final decision on this difficult problem will only be reached by the demonstration of the organisms in later stages of the disease process.

The second point of special interest concerns the ætiology of our cases. The distribution of the inflammatory change was different from that generally regarded as characteristic of the chronic pathological residuals of lethargic encephalitis (Spatz, 1930 ; Stevenson, 1942). Most authors have found that in the latter the acute as well as the residual changes are most severe in the substantia nigra and in the grey matter around the posterior end of the third ventricle, the aqueduct, and the upper end of the fourth ventricle. They are less severe in the globus pallidus, and usually negligible in the rest of the basal ganglia and the cerebral cortex. In Case 1 only the lesion of the substantia nigra approximated to that seen in the chronic form of lethargic encephalitis, but this case was atypical because of the heavy involvement of the cerebral cortex and, in particular, of the cerebral white matter, which brings it into the type of leuco-encephalitis recently described by van Bogært (1945). The wide distribution of the inflammatory change in all our cases resembles encephalitis of the equine, St. Louis, Japanese, and herpetic varieties more than the von Economo type. Case 3, with its combination of diffuse and focal changes comes particularly close to the description of extra-European epidemic encephalitis (Uchiyama, 1925 ; Weil, 1934 ; Farber

and others, 1940 ; Noran and Baker, 1943 ; Hassin and Rabens, 1944). These varieties of encephalitis have not yet been reported in Great Britain. It is interesting that Noran and Baker have found that the Western equine type occurs in a chronic form. This has not yet been shown for the other types mentioned. Analysis of individual cases on a clinical and morphological basis, as has been done in this paper, cannot be expected to settle the problem of ætiology, a problem that can only be solved by attempting to identify the ætiological agent, by actually isolating it from the brains of patients dying of encephalitis, or by demonstrating the presence of specific neutralizing antibodies.

In 1933, Dawson described a case of encephalitis occurring in a child, and running a course of several months, in which intranuclear inclusion bodies were found. A similar case was later described by Akelaitis and Zeldis (1942). Two such cases have been reported in Great Britain (Brain and others, 1943). All cases so far described have occurred in children and have run a subacute course of two to six months. My Cases 1 and 3 correspond to this description, but such a diagnosis is ruled out by the absence of inclusion bodies.

Finally, we must mention again that, although a positive iron reaction is certainly more characteristic of paresis than of any other condition (for example, see Jahnel, 1930 ; Galbraith, 1938) our Case 2 supports the statements of Kingo (1934), Uchiyama (1925), Scholz (1923) and von Economo (1920), that it may be encountered in other inflammatory diseases.

Summary

Three cases of encephalitis are described. All were insidious in onset and progressive in course over periods of time varying from four months to five years. Pathologically they were characterized by intense inflammatory changes widely distributed throughout the brain. The possible ætiology is discussed in each case. Case 1 was distinguished by a particularly severe involvement of the cerebral white matter which closely resembles the "*leuco-encephalite sclerosante subaigue*" of van Bogært. The second case had a positive iron reaction. In the third there was the combination of diffuse and focal cystic lesions characteristic of some of the extra-European types of epidemic encephalitis.

My thanks are due to the Superintendents of the Crighton Royal Hospital, Dumfries, the Leavesden Hospital, Hertfordshire, and Cane Hill Hospital, Coulsdon, Surrey, for the clinical data of these cases. I am grateful to the London County Council for permission to work in the teaching and research laboratory of the Maudsley Hospital, and to the staff of the Laboratory, particularly to Dr. Alfred Meyer who suggested this investigation and gave advice in the preparation of the paper. I am also grateful for helpful criticism offered by Dr. J. G. Greenfield.

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SENSORY DISTURBANCES OCCURRING IN SCIATICA DUE TO INTERVERTEBRAL DISC PROTRUSIONS: SOME OBSERVATIONS ON THE FIFTH LUMBAR AND FIRST SACRAL DERMATOMES

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IT is now widely accepted that many cases of severe and persistent sciatica are due to compression extrathecally of either the fifth lumbar nerve root by a protrusion from the fourth lumbar intervertebral disc, or the first sacral nerve root by a protrusion from the fifth lumbar disc (Bradford and Spurling, 1941; Falconer, 1944; etc.). It is also known that, in such cases, areas of sensory impairment, particularly of pain and tactile sensibility, often appear in the affected leg. These areas, however, are difficult to chart, for the sensory loss is only partial, and it is generally assumed that they are confined to the foot and leg below the knee. In fact some authorities (Love and Walsh, 1938; O'Connell, 1943) presume that, if sensory changes extend above the knee, more than one nerve root must be involved, and that sacral roots within the theca are affected as well as the extrathecal nerve root at the level of the disc protrusion. Few appear to realize that, if sensation is tested carefully, a slight disturbance can usually be detected in the thigh and buttock as well as below the knee, even though only a single nerve root is involved, and that by careful study of these areas of sensory disturbance it is often possible to identify the exact nerve root concerned. Until a late stage in our own experience we did not realise that compression of either of these two nerve roots commonly produces patterns of sensory impairment which extend well above the knee. We then learnt that, if sensation is tested in a simple but standardized manner, it is frequently possible to outline a pattern of sensory change (verifiable by other examiners) which is characteristic of the particular nerve root, and hence is of diagnostic value. Since then further observations have been made which indicate that these areas are in reality dermatomes, and that the classical descriptions of the dermatomes by Head (1893), Déjerine (1914), and Foerster (1933), and even the more recent description by Keegan (1943) are faulty. Our observations instead support and expand ideas on these particular dermatomal areas put forward by Thorburn in 1893. We have also observed that areas of hyperalgesia may occur within the dermatomes, and further that, when pain is severe, sensory impairment may become more extensive than can be explained on a segmental basis alone.

Method of Sensory Examination

Patients suffering from sciatica, who were admitted to the Neurosurgical Department of the Dunedin Hospital, New Zealand, were examined pre-operatively. Usually the symptoms had not been relieved by complete rest in bed for one month or longer, and were still sufficiently disabling to interfere with the patient's activities. Some had such severe pain as to be unable to rise from bed, but for the most part they were able to walk, although with discomfort. All cases were later proved at operation to be suffering from nerve root compression by a disc protrusion.

Like other observers, we found that sensory disturbances are detected more readily by painful than by other stimuli. Our method of examination was simple, and the only instrument required was a sharp needle or pin, or preferably a surgical needle mounted on a fine spring which, if compressed each time to the same degree, enabled stimuli of uniform intensity to be applied. The examination began with a series of pricks placed circumferentially a quarter to half an inch apart, first round the foot and then round the leg. The patient was prevented from watching what was going on. In this way the presence of any zone in which sensibility was not quite as acute as elsewhere, or was otherwise different, was determined. A test on the unaffected leg or on an upper limb acquainted the patient with the normal degree of pain produced by the standard stimulus.

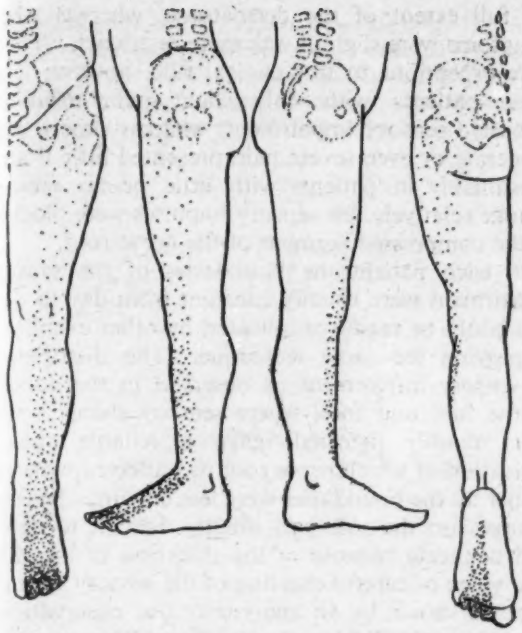

FIG. 1.—Pattern of area of hypoalgesia corresponding to the fifth lumbar dermatome.

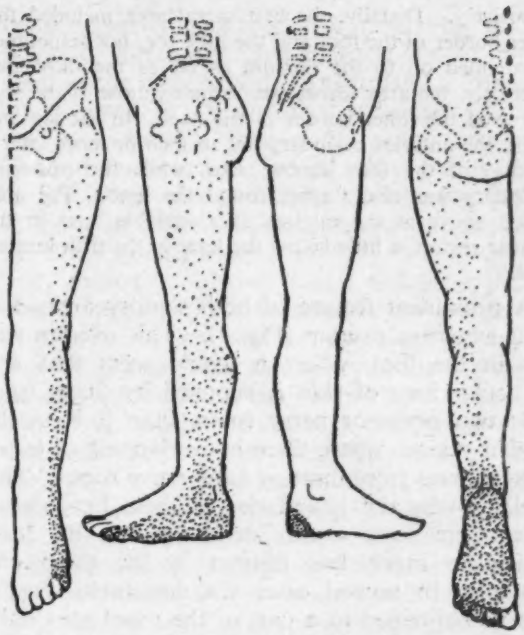

FIG. 2.—Pattern of area of hypoalgesia corresponding to the first sacral dermatome.

Once a zone of hypoalgesia was discovered, all further testing was done from its interior outwards toward the normal skin, so that the boundaries might be determined. Tests had to be quick, with each series of pricks coming in rapid succession so that the patient did not tire. The patient signalled the moment he felt a change in the intensity of sensation, and the point at which this occurred was marked on the skin. When one boundary had been thus determined, the next was at once sought by applying the stimuli in a parallel or slightly radial direction half to one inch away. With practice the examiner could usually plot an area of sensory disturbance quickly. A good deal depended, however, upon the patient's perceptive ability, as the diminution in sensation was only slight, and not marked as in a peripheral nerve injury. The patient could usually distinguish readily between the blunt and sharp ends of a pin over the whole zone of hypoalgesia, and the only change he would notice was that at the boundary the prick of the pin suddenly became a little more vivid. We found that if the type of change to be expected was first explained to the patient the sensation could usually be tested successfully, but that if he were uncertain or apprehensive his replies would become misleading and even contradictory.

Observations

By employing this simple method of testing we noted three distinct types of sensory disturbance. Most often, a zone of hypoalgesia affecting a single dermatome extended along the lateral aspect of the limb from the foot to the buttock, its boundaries varying according to the nerve root involved. Sometimes, however, there were areas of hyperalgesia within the dermatome. And occasionally there was a condition of "spreading hypoalgesia" in which sensory impairment was much more extensive than could be accounted for on a dermatomal basis alone. Each set of observations will be described in turn.

Dermatome Hypoalgesia.—Hypoalgesic areas were detected in 33 out of 50 consecutive patients. These areas conformed to one or other of two main patterns and usually approximated to the full extent of the pattern, although sometimes they represented only its distal part. Each pattern was characteristic of a particular nerve root.

FIFTH LUMBAR NERVE ROOT LESIONS.—This area involved a strip, from three to six inches wide, stretching from the foot to the lumbar region (Fig 1). At the foot it usually occupied the dorsum and the middle three toes, but sometimes it extended on either side to include the big and little toes, although it always spared the inner and outer borders of the foot. Inferiorly, it involved a wedge-shaped area of the sole. Above, it included the lateral surface of the leg, where its anterior boundary ran along the medial surface of the tibia. On the thigh it went in a gradual spiral on to the posterior surface, and then crossed the buttock to end in the lumbar region at the midline and at a variable level.

FIRST SACRAL NERVE ROOT LESIONS.—This area resembled the fifth lumbar area in its general form, but it lay more laterally in the foot and leg and at a lower level in the lumbar region (Fig. 2). The two areas overlapped

extensively. Distally, the first sacral area included the outer border of the foot and the little toe, but sometimes it extended on to the dorsum as far as the third toe. Inferiorly, the area sometimes included most of the sole and even the inner border of the heel. In the leg and thigh, the anterior boundary lay an inch or more lateral to that of the fifth lumbar area, while the posterior boundary was also further round the limb. The area ended above at the midline at a variable level in the lumbar region, a little below the level of the fifth lumbar area.

A prominent feature of both sensory areas was their extensive overlap (Fig. 4). This overlap was less in the foot, where it would seem that any particular area of skin is supplied by fibres from only two posterior nerve roots, than it is in the lumbar region, where there is overlapping distribution of fibres from three or more nerve roots. This explains why the boundaries of these hypoalgesic areas were most readily determined in the foot, and were much less distinct in the thigh and buttock. In several cases the detectable sensory loss was confined to a part of the usual area only, namely, to the foot and leg. This fluctuation in boundaries, particularly evident in the more proximal areas, was presumably due to variations in blocking of sensory impulses in the nerve root at the site of compression. When symptoms of sciatica were marked, the area of spontaneous hypoalgesia was usually large and approximated to the full extent of the dermatome, whereas when symptoms were slight it was more restricted. There were exceptions to this clinical rule, however, and some patients with only slight pain exhibited extensive sensory impairment, whereas others with moderate or even severe pain presented little if any. Presumably in patients with little or no sensory change relatively few sensory impulses were blocked in the compressed segment of the nerve root.

In each patient the boundaries of the sensory impairment were usually constant from day to day, and could be readily duplicated by other examiners employing the same technique. The distribution of sensory impairment as observed in the dorsum of the foot and toes, where sensory changes were most readily detected, gave a reliable clinical indication of which nerve root was affected, whereas higher up the boundaries were less certain. Sensory changes on the sole was usually difficult to detect and delineate because of the thickness of the skin. The value of careful charting of the sensory disturbances is shown by an analysis of our observations, as given in the Table. In a series of 50 consecutive patients with sciatica due to intervertebral disc protrusions, 11 showed hypoalgesic areas in the toes and dorsum of the foot conforming to the first pattern (fifth lumbar dermatome), and 21 showed areas conforming to the second pattern (first sacral dermatome). In all instances the identity of the nerve root which was presumed to be involved was later confirmed at operation, thus showing the accuracy of the sensory testing. In one case the area of spontaneous hypoalgesia seemed to involve the territories of both the fifth lumbar and the first sacral nerve roots, and at operation disc lesions were found at two different levels, each compressing one of these roots. In addition, 3 patients showed "spreading hypoalgesia," while 14 had either no sensory disturbance, or changes so slight and inconstant that they could not be charted.

TABLE

Type of disturbance	Number affected
Dermatomal hypoalgesia	33
"Spreading hypoalgesia"	3
Hyperalgesia within a dermatome	0*
No detectable sensory disturbance	14
Total ..	50

Subdivision of cases showing dermatomal hypoalgesia	L 5 dermatomes	S 1 dermatomes
Complete pattern	9	17
Incomplete pattern	2	4
Total ..	11	21
	Plus 1 case of combined L 5 and S 1 dermatomes	

Analysis of sensory disturbances in 50 consecutive cases of sciatica, caused by lumbar intervertebral disc protrusions, later verified at operation.

* The three cases of hyperalgesia within the dermatome which are described in the text were collected before the present series of 50 consecutive cases was begun.

Procaine Block.—In a few patients we succeeded in blocking with procaine solution the fifth lumbar and first sacral nerve roots immediately lateral to the theca, producing areas of hypoalgesia, which presumably were of dermatomal character (a dermatome being defined as the area of skin supplied by a single posterior nerve root). These areas of induced hypoalgesia were essentially similar to those occurring spontaneously in sciatica.

The method consisted of insertion into the theca in the midline of a fine-bore lumbar-puncture needle at either the fourth or the fifth lumbar interspace. Using this needle as a guide to the depth and direction of the theca, a second needle was inserted parallel to it and

approximately half an inch to one side (Fig. 3). As the point of the second needle passed inwards, it could be felt to pierce the ligamentum flavum, and then, when about half an inch deeper than the guide, it came into contact with the nerve root just after it left the theca.

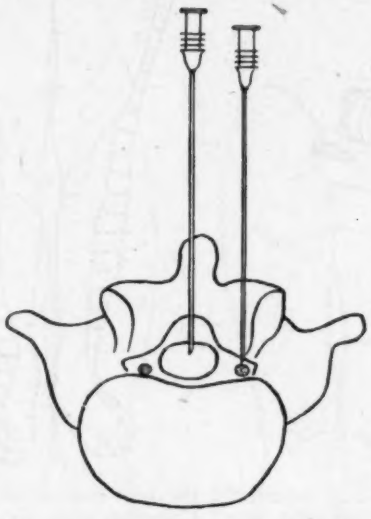

FIG. 3.—Position of needles placed for infiltration of an extrathecal nerve root with local anæsthetic solution. The central needle serves as guide. The lateral needle is employed for injection.

If the needle was correctly placed, movement of it caused severe pain referred to the leg, indicating that the nerve root was impinged upon, and if the stilette was removed no cerebrospinal fluid escaped. Once the needle was in position, 0·5 c.cm. of 5% procaine solution containing a trace of adrenaline was injected, followed five minutes later by a second injection of the same amount. By employing procaine in small amounts of high concentration, its effects could be limited to the nerve root being tested.

On account of the difficulty in placing the needle correctly, especially in heavily-built persons, it was not always possible to make a successful injection. If the injection was technically successful, the patient usually remarked within a few minutes that his leg was becoming numb, while at the end of ten minutes, when the block was complete, there was a definite zone of hypoalgesia together with weakness of ankle movements and, in the case of the first sacral nerve root, absence of the ankle jerk. Injection at the fourth lumbar interspace blocked the fifth lumbar nerve, and injection at the fifth space blocked the first sacral. If the nerve root infiltrated was the one compressed, the patient was relieved of pain, and the straight-leg-raising movement was no longer limited. In fact these tests can be used to identify pre-operatively the affected nerve root, but, as they are difficult to perform, they are of academic rather than of practical value.

The areas of hypoalgesia produced by this root-infiltration technique were almost identical with those occurring spontaneously in sciatica, the only points of difference being that the sensory impairment in the induced areas was usually a little more intense, and the boundaries, although similar in the foot, were a little wider apart proximally. These differences were small, and probably due to the local anæsthetic blocking all the sensory fibres in the root, whereas in compressive lesions some of the fibres usually escape.

By means of this infiltration technique we were able in some patients to produce nerve-root block in the sound leg, and to compare the induced sensory change with the spontaneous hypoalgesia existing in the affected leg. When the corresponding nerve root had been infiltrated, the two areas were essentially similar. By injecting the fifth lumbar nerve on one side, and the first sacral on the other in a case of low back pain without spontaneous sensory loss, we were able to induce a fifth lumbar dermatome hypoalgesia in one leg simultaneously with a first sacral dermatome hypoalgesia in the other, and so to control some of our other observations. This case exhibited clearly overlap of the two dermatomes (Fig. 4).

As a result of these observations with artificially produced nerve-root blocks, there can be little doubt that the areas which occur spontaneously in sciatica are in reality dermatomal areas.

Hyperalgesia within Dermatomal Areas.—In three patients an exaggerated response to the standard pain stimulus was observed within a dermatomal area. In two of these the area of hyperalgesia was confined to the buttock, below which it was continuous with a hypoalgesic area occupying the distal portion of the dermatome. In these two cases the increased reaction could be demonstrated only by pinprick, no change being found to tactile or thermal stimuli. In the third case the area of exaggerated pain response was larger, extending from the buttock as a narrow band down to the dorsum of the foot in the territory of the fifth lumbar nerve root. Within this area were smaller areas showing increased reaction to heat and to light touch. No definite change to cold stimulation was appreciated. Below the area of hyperalgesia there was a small patch of hypoalgesia along the outer part of the foot. An interesting and significant observation was made in this third patient after the fifth lumbar nerve root had been blocked extrathecally with procaine solution by our root-infiltration method. As the block developed, the increased reactions to pinprick, heat, and touch disappeared, and were replaced by a typical hypoalgesic dermatome. Later at operation, in this patient as in the other two, a disc protrusion was found compressing the anticipated nerve root, and was removed. We conclude from these observations that sometimes areas of hyperalgesia may develop within dermatomes, and that, when present, they tend to appear in the proximal part of the dermatome rather than in the distal. They may be

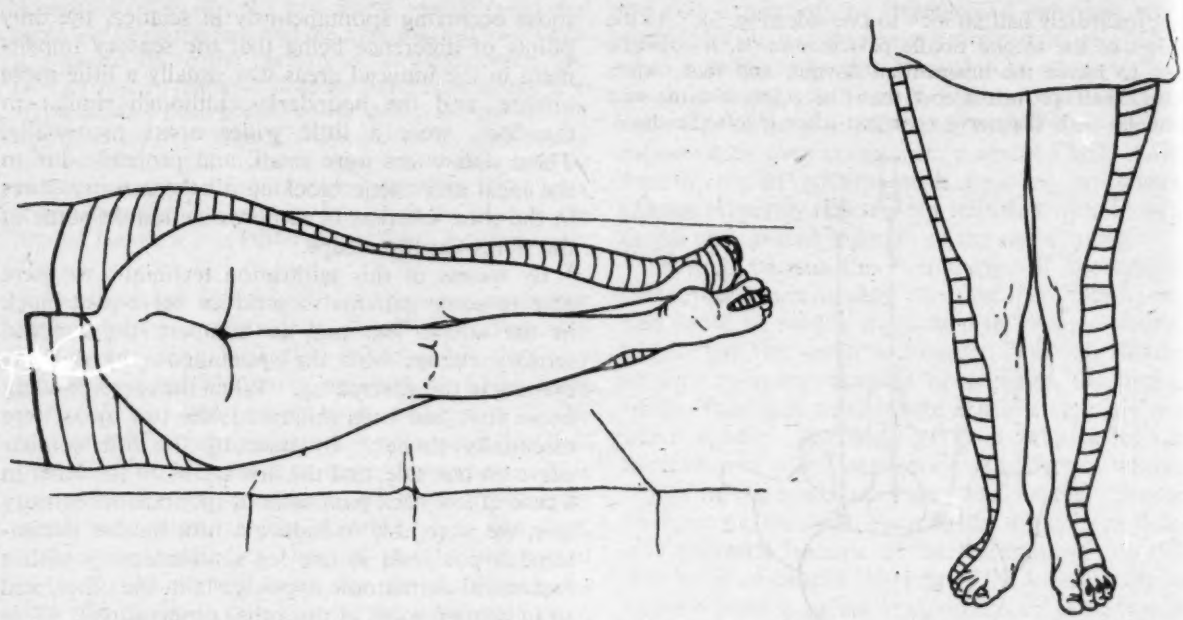

FIG. 4.—Extent of hypoalgesia produced by blocking with a local anæsthetic the fifth lumbar nerve root on the left side and the first sacral nerve root on the right side. Compare with Figs. 1 and 2. Note the degree of overlap.

associated with hypoalgesia in the distal part of the dermatome.

"Spreading Hypoalgesia."—Three patients, all confined to bed with sciatic pain, all had areas of hypoalgesia far more extensive than the distribution of a single nerve root. This extensive hypoalgesia was associated with marked weakness of all movements of the limb, and with gross limitation of straight-leg raising. In one case the hypoalgesia involved the whole hindquarter, its upper boundary fluctuating between the umbilicus and the costal margin (Fig. 5). In the other two, most of the lower limb below the groin was affected. Yet in all three at operation only a single disc protrusion was found compressing a single nerve root (the first sacral), and furthermore all symptoms and sensory signs completely disappeared after its removal.

In one case an observation was made which throws some light on the mechanism of " spreading hypoalgesia." The affected nerve root (first sacral) was infiltrated preoperatively with procaine solution according to our usual technique. This resulted in disappearance of the patient's pain for more than half an hour, and also of the limitation of straight-leg raising, while the motor power became nearly normal. While the procaine block was operating, a suspicion of a hypoalgesic zone encircling the lower abdomen persisted, but elsewhere in the lower limb the skin outside the boundaries of the first sacral root area now had normal sensibility. In other words, when the patient's pain was relieved, the superadded features of extensive motor weakness and of extensive sensory loss disappeared, leaving only those of a simple nerve-root block. The significance of this observation will be considered later.

Discussion

As a result of these various observations it seems evident that the sensory changes present in sciatica are usually due to compression of a single nerve root either the fifth lumbar or the first sacral. In some cases there are no detectable sensory signs, presumably because there is little or no interruption of sensory nerve impulses at the compressed segment of the nerve root. In the majority of patients however, areas of sensory impairment of a dermatomal pattern are encountered. In a few instances areas of hyperalgesia may be met with, which usually involve the proximal portion of a dermatome and are often associated with hypoalgesia in the distal portion. In a further small group with severe spontaneous pain, the area of sensory loss may extend far beyond the anatomical confines of individual dermatomes.

Although current teaching based on Fœrsters' observations (1933) is that no sensory disturbance follows the interruption of a single posterior nerve root, this has not been our experience, nor that of Déjerine (1914). Fœrster, however, was apparently not concerned with the finer degrees of sensory impairment which we have charted, but rather with areas of complete sensory loss. We agree with his observations that nowhere is cutaneous sensation abolished after interruption of only one posterior nerve root, but we have found that there is a slight

diminution of its intensity within the segmental boundaries. As our dermatomal areas differ from those previously described, it seems appropriate at this stage to outline the classical descriptions of the dermatomes and the basis on which they were derived.

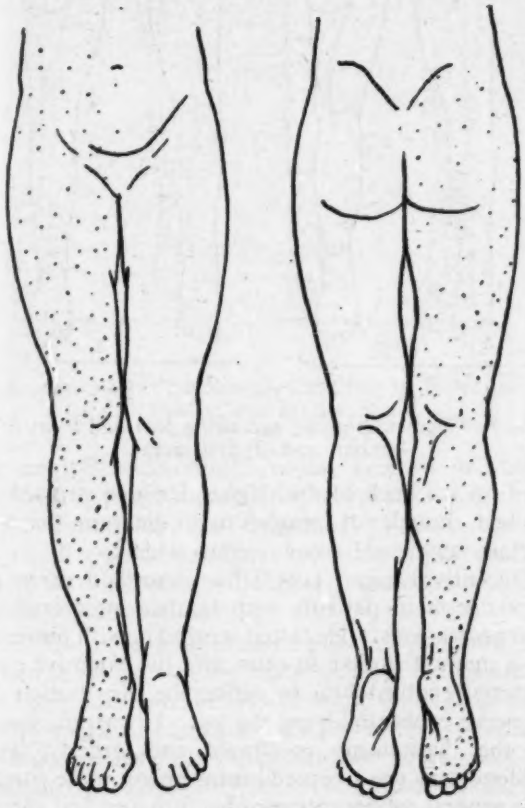

FIG. 3.—Extent of sensory impairment in a case of "spreading hypoalgesia" due to compression of the first sacral nerve root.

Classical Descriptions of Dermatomes.—The classical dermatome charts are based upon the work of Head (1893) and of Fœrster (1933) on man, and of Sherrington (1893) on the monkey. The boundaries of the fifth lumbar and first sacral dermatomes are similar in the schemes of Head and of Fœrster, but with one essential difference. Fœrster demonstrated extensive overlapping of his segmental areas, whereas Head found none, even on the trunk. In both schemes the fifth lumbar and first sacral dermatomes are confined to the leg and foot, and do not extend above the knee. In Fœrster's scheme (Fig. 6) the fifth lumbar dermatome occupies the whole anterior aspect of the leg, the dorsum of the foot, and also the medial part of the plantar surface of the foot. Head's boundaries (Fig. 7) are less extensive, for they do not include the toes or the sole of the foot. Fœrster described the first sacral dermatome as involving the greater part of the sole and the outer border of the foot, as well as an area on the posterolateral part of the leg. Head includes in addition the dorsum of all the toes. Fœrster arrived at his dermatomal areas by applying to man the method of residual sensibility employed by Sherrington in the monkey. As a therapeutic measure for various painful conditions, he divided a series of posterior nerve roots above and below a single posterior nerve root which he left intact. Subsequently he was able to chart between two areas of apparent analgesia an area of remaining sensibility, which he presumed to be a dermatomal area. By this method Fœrster in the course of operations upon many patients was able to outline what appeared to be the distribution of each posterior nerve root. At first sight this would seem to be a most accurate method of outlining the distribution of a nerve root, but reasons will be given later for believing that this is not so. Head outlined the distribution of skin lesions in cases of herpes zoster, and subsequently fixed the segmental level of his areas, by correlation with areas of sensory loss observed in cases of traumatic lesion of the spinal cord at known levels. His areas do not overlap, and it is interesting that Head himself did not claim them to be dermatomes. He was conversant with the early work of Sherrington, who had shown in the monkey that dermatomes as determined by the method of remaining sensibility do overlap. Head deduced that the areas he had mapped corresponded "to the supply, not of roots, but of segments of the spinal cord from which the roots in part arise." It has been left to subsequent writers to assume that Head regarded his areas as dermatomes.

Neither of these investigators made any attempt to correlate the arrangement of dermatomes in the limbs with that in the trunk. The result is an unconvincing, and apparently haphazard, arrangement of patches of skin with no underlying scheme. To bring the arrangement of dermatomes in the limb of the monkey into line with that in the trunk, Sherrington (1893) introduced the concept of anterior and posterior axial lines, regarded as "branches" of the mid-dorsal and mid-ventral lines entering the limb. On this basis he explained the fact that in the monkey, as in man, the roots in the centre of the plexus supplying a limb seemingly were not distributed to the proximal part of the limb. Déjerine (1914) rationalized the ideas and observations of other workers, and applied this concept of Sherrington to dermatomes in man. His chart is now widely used. When it is recognized

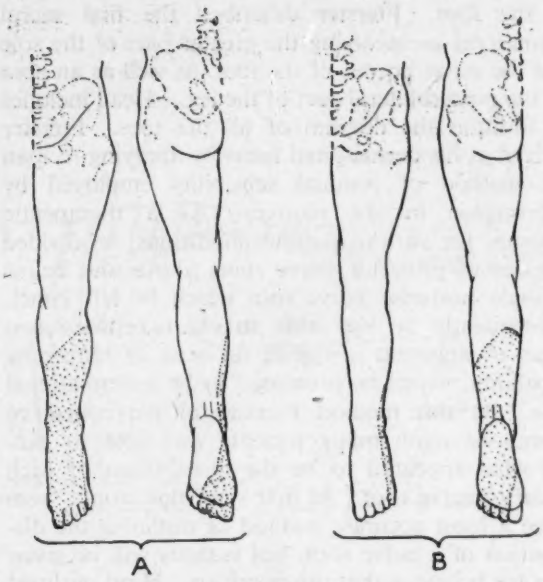

FIG. 6.—Extent of dermatomes, according to Fœrster: (*a*) fifth lumbar, and (*b*) first sacral.

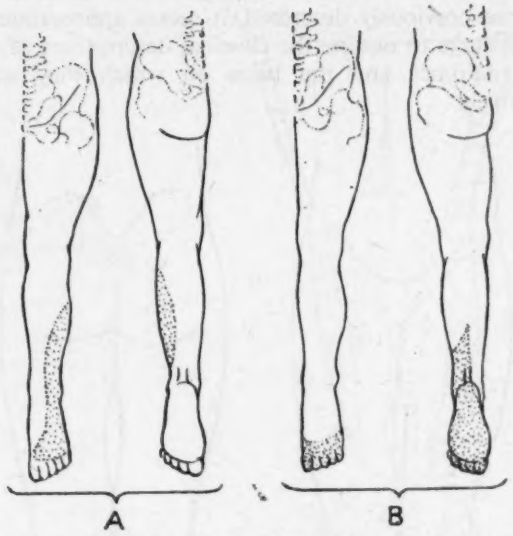

FIG. 7.—Segmental areas, according to Head: (*a*) fifth lumbar, and (*b*) first sacral.

however, that all limb dermatomes extend to the mid-dorsal line, the need for postulating Sherrington's axial lines disappears.

Thorburn (1893) in a critique of Head's paper described views on the sensory distribution of the various spinal nerves, which, as regards the fifth lumbar and first sacral nerves, are very similar to our own. It is a great pity that his paper has not been given the attention which it deserves. Thorburn studied areas of sensory loss in patients with disease or injury affecting known and limited regions of the spinal cord, or of isolated nerve roots, and he collected both personal observations and observations recorded in the literature. From these observations he deduced the segmental supply of various spinal nerves, by subtracting from the anæsthetic areas in his cases those areas whose nerve supply had already been established by anatomical dissection or otherwise. In this way he arrived at the areas of distribution of the remaining nerves. His method had obvious limitations, for it was dependent upon a sufficient supply of suitable clinical cases. By this means, however, he drew up a chart, which shows a distribution of the fifth lumbar and first sacral nerves that in many respects resembles our own (Fig. 8). He stressed that both these segmental areas, in addition to their distribution below the knee, extended upwards along the whole length of the thigh. He was unable to ascertain just how high they extended above this, and, largely on theoretical grounds, he depicted them in his chart as embracing the second sacral area on the back of the thigh. He also stressed in his text, though not so much in his diagram, that the various segmental areas overlap widely.

Recently Keegan (1943) has described areas of hypoalgesia in patients with lumbar intervertebral disc protrusions. He tested sensibility with pinprick by a method similar to ours, and his extensive case material enabled him to define the distribution of all nerve roots supplying the leg. His arrangement of the dermatome is simple and orderly, and analogous to the accepted arrangement in the trunk. The general configuration of his fifth and first sacral dermatomes (Fig. 9) is similar to those we have observed, but our findings differ in an important respect. There is no overlap in Keegan's charts, although he admits that the skin supply of each root may be greater than he shows.

The Anatomical Basis of Cutaneous Pain.—It has been well shown that the primary sensations of pain, touch, heat, and cold are each represented on the skin in punctate form (Walshe, 1942; Weddell, 1945). Underlying each spot, which is sensitive to touch, heat, or cold, are a group of specific structures, such as Meissner's corpuscles and Merkel's discs for touch, Ruffini's endings for heat, and Krause's end-bulbs for cold, each group of structures being innervated by at least two different medullated nerve fibres. In the case of pain however, there are no comparable structures, but instead plexuses of myelinated and unmyelinated fibres situated in the dermis form the basis of the peripheral receptor mechanism. These plexuses give rise to

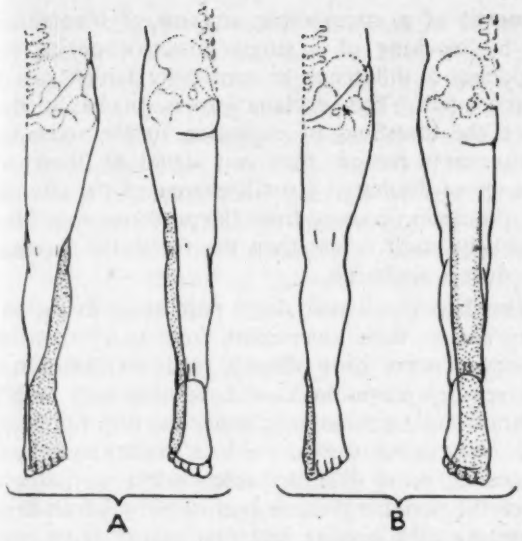

FIG. 8.—Extent of dermatomes, according to Thorburn : (*a*) fifth lumbar, and (*b*) first sacral.

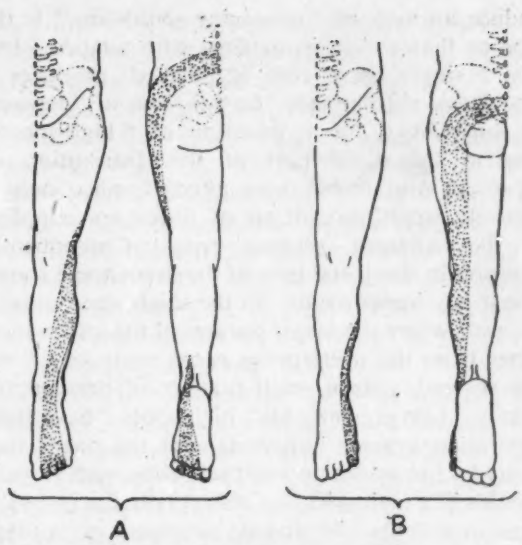

FIG. 9.—Extent of dermatomes, according to Keegan : (*a*) fifth lumbar, and (*b*) first sacral.

fine unmyelinated fibrils which end in beaded terminals that are situated in the dermis and the deeper layers of the epidermis. Within these plexuses it would seem that the branches from each parent fibre interlock with those from other fibres, but do not anastomose.

It is difficult to demonstrate a punctate distribution of pain in all parts of the body with a stimulus such as a pinprick, but Bishop (1944a), employing an electric spark of constant intensity as his stimulus, was able to show clearly that there are " high-spots " of sensitivity scattered over the skin, and that each is surrounded by an area of lower threshold 2 to 15 mm. diameter. By histological methods Bishop showed that each " high-spot " is supplied by branches from a number of fibres (Bishop, 1944b). He also found, when investigating the area of overlap of adjacent cutaneous nerves, that the response of a " high-spot " lying in the area of overlap may be lowered if one of the nerves supplying the area is blocked with a local anæsthetic. This indicates that the nerve fibres supplying a " high-spot " may come from different cutaneous nerves, and also that the response of a " high-spot " to a given stimulus depends on the number of nerve fibres which are functioning.

If we postulate that the nerve fibres may come not only from separate cutaneous nerves but also ultimately from separate posterior nerve roots, dermatome hypoalgesia would be explicable by a diminution in the number of functioning nerve fibres supplying the pain " high-spots " within the territory of the affected posterior nerve root. Our observations have shown that the overlap of the fifth lumbar and first sacral dermatomes is greatest proximally and least distally, and this can be correlated with the observation that sensory impairment is most vivid distally and least vivid proximally. Thus in the foot and leg, where each particular area of skin is innervated from approximately two posterior nerve roots, though not necessarily in equal proportions, a complete block of the nerve root affording the major supply will eliminate a high proportion of sensory fibres coming from the various " high-spots," and consequently will produce an appreciable degree of hypoalgesia. On the other hand in the thigh and buttock, where each particular area of skin is situated within the territory of three or more posterior nerve roots and presumably is supplied from each of them, blocking of one posterior nerve root will involve a much smaller proportion of the nerve fibres coming from the " high-spots," and so the resulting sensory impairment is less. Another factor contributing to the same result is that the component fibres of the fifth lumbar and first sacral nerve roots are probably distributed with a greater density in the distal parts of their dermatomes than in the proximal.

In contrast to the condition of dermatome hypoalgesia is the state of affairs existing when either the fifth lumbar or first sacral nerve root remains intact, while several above and below have been divided. This is the basis of the method employed by Sherrington and by Fœrster for determining the extent of the dermatomes. The number of nerve fibres which are left functioning after this procedure, and which

produce an area of " remaining sensibility," is the same as that which, in patients with sciatica when only a single nerve root is blocked, produces a hypoalgesic dermatome. In this state of " remaining sensibility " the innervation of " high-spots " lying in the distal part of the distribution of the intact root is but little affected, since only a relatively small proportion of fibres are supplied by the adjacent severed roots. Consequently sensation in this distal part of the dermatome shows little if any impairment. In the thigh and buttock, however, where the major portion of the innervation comes from the overlapping nerve roots which are now severed, only a small number of nerve fibres remain. Consequently all " high-spots " have their innervation gravely impaired, with the result that it may be impossible to elicit sensation with a weak stimulus like a pinprick. Cobb (1919), for instance, found in patients with divided cutaneous nerves that near the margins of areas of sensory loss there are zones which are insensitive to a pinprick of 15 g. weight, but which are sensitive to a pinprick of 30 g. weight. These zones, which at first sight appear analgesic, are therefore in reality deeply hypoalgesic, and the areas in the thigh and buttock after isolation of either the fifth lumbar or first sacral nerve roots can probably be compared to them. These are the areas which we think represent the proximal portions of the dermatomes. Had Fœrster employed a massive stimulus, such as a hot disc of metal instead of a pinprick, he might have aroused sensation in these areas.

It is probable, then, that a pinprick may not be perceived in an area from which a large proportion, but not all, of the nerve supply has been removed. It has been shown that summation of the excitatory effects of a number of afferent nerve fibres is necessary before a reflex discharge is set up in an anterior horn cell (Eccles and Sherrington, 1930). Presumably the response of the secondary neurones in the pain pathways requires similar summation, and these neurones, like the anterior horn cells, have large numbers of terminations from different afferent nerve fibres in contact with them. Consequently, when a large proportion of the afferent nerve supply from any given area is out of commission, the few impulses which reach the spinal cord through the intact nerve fibres are unable to make the secondary neurones discharge. In addition it is probable that summation of many impulses is also necessary for the tertiary relay of the pain pathway. Granted then that impulses arising from stimulation of an area of little residual sensibility may not reach consciousness, we have still to explain why in the opposite circumstance removal of a comparable amount of innervation, as by blocking of a single posterior nerve root, produces a difference in sensibility which can be appreciated. The explanation is probably that, once the threshold of excitation in the secondary neurones is passed, they can signal by their frequency of discharge a small change in the intensity of stimulation coming from the posterior root fibres which by itself is less than the threshold necessary to cause a discharge.

Our hypothesis that single pain spots in the skin may receive their innervation from more than one posterior nerve root offers a ready explanation of the sensory phenomena we have observed, both in sciatica and after blocking either the fifth lumbar or the first sacral nerves with a local anæsthetic. However, some difficulty arises when we come to trace the peripheral nerve pathways by which fibres from the fifth lumbar and first sacral nerve roots reach the various parts of their respective dermatomes. The fibres which supply the leg below the knee are undoubtedly conveyed by the great sciatic nerve (fourth and fifth lumbar, and first, second, and third sacral nerves) and its branches. The pathway to the buttock is probably by way of the posterior primary divisions of the spinal nerves. The 1938 edition of Gray's *Anatomy* describes the posterior primary divisions of both the fifth lumbar and first sacral nerves as possessing branches which help to supply the skin over the posterior aspect of the buttock. The first sacral nerve is undoubtedly conveyed to the posterior aspect of the thigh by the small sciatic nerve (posterior femoral cutaneous nerve—first, second, and third sacral). But it is difficult to see at first sight how the fifth lumbar nerve is conveyed to the thigh, because in the conventional descriptions of British anatomical textbooks the fifth lumbar nerve is excluded from the small sciatic nerve, and so from the cutaneous innervation of the thigh. The French anatomists, however, provide a way out of this dilemma, for they (Testut, 1930) describe the inferior gluteal nerve (fifth lumbar, and first and second sacral) and the small sciatic nerve (first, second, and third sacral), not as two separate nerves as their British confrères do, but as a single nerve which gives motor branches to the gluteus maximus muscle and sensory branches to the posterior aspect of the thigh and buttock.

Finally, we have to account for the marked overlap of distribution of the fibres of neighbouring nerve roots once they reach the skin. Our observations have shown clearly that, in the leg, the fifth lumbar and first sacral dermatomes occupy broad zones, each covering a large part of the circumference of

the limb. Similarly, the dermatomes of the trunk are probably also broad, for we have observed a zone of hypoalgesia from three to three and a half inches wide, encircling one side of the chest, after division of only a single posterior nerve root (the fourth thoracic). In considering why the dermatomes are so broad, the arguments of Tower (1943) bearing upon the area of distribution of a single pain fibre should be remembered. She has pointed out that the spreading cutaneous hyperalgesia of Lewis, which is seen after pinching, faradizing, or otherwise injuring a small area of skin, would be explicable without the necessity of assuming a special nocifensor system of innervation, if a single pain fibre were distributed over a much larger area than most authorities have hitherto believed possible. She is prepared to postulate unit areas in the skin of the human forearm measuring nine to twelve cm. long by three to four wide. Her concepts have yet to be confirmed or refuted by other methods, but, if they are true, they will help considerably in the understanding of the mechanisms of overlap between two dermatomes.

Fœrster stimulated at operation the distal ends of various posterior nerve roots which he had divided, in an attempt to mark out segmental areas by observing the extent of the resultant cutaneous vasodilatation (the "antidromic" response of Stricker and Bayliss). Lewis (1942) quotes him as noting that this caused a burning sensation to appear in the area of overlap of other roots. The conditions under which Fœrster made his observations are paralleled by those seen in nerve-root compression. In this latter condition the conduction of impulses through the affected root can be assumed to be blocked, while impulses probably arise at the damaged region and pass centrifugally down the nerve to the periphery. According to Lewis' hypothesis, the centrifugal impulses on reaching the terminations of the pain fibres cause liberation in the skin of a pain-producing substance (P substance), which lowers the threshold of the pain endings of the overlapping roots and produces hyperalgesia. It is significant for this explanation that in each of our three cases the hyperalgesia appeared in the proximal regions, where overlap from the neighbouring nerve roots is greatest.

The phenomenon of "spreading hyperalgesia" cannot be explained on known anatomical grounds, for the areas it involves extend both far above as well as far below the segmental level of the affected nerve root. In each of our three cases, "spreading hypoalgesia" was associated with pain of marked severity. Another noticeable feature was widespread motor weakness. It is significant that, after pain had been relieved by operative removal of a single nerve-root compression, the "spreading hypoalgesia," as well as the widespread motor weakness, disappeared in all three cases. It is also significant that both these features disappeared temporarily in our third case, when pain was relieved by a procaine block of the affected nerve root. These observations suggest that the severe pain, itself, is the factor responsible for "spreading hypoalgesia." Ray and Wolff (1945) have shown clearly that with pain of great severity the afferent impulses may spread widely within the spinal cord, thus affecting neurones with which they are not normally in functional communication. Their evidence is that in a patient with a unilateral loss of pain sensibility due to an anterolateral chordotomy, the application of a severe nocuous stimulus to the analgesic limb causes the patient to feel pain at the comparable point in his opposite sound limb. We have in part confirmed their observations, and the only likely explanation is that the intense bombardment by the incoming pain impulses excites widespread discharges of internuncial neurones, and hence eventually of the secondary neurones of the pain pathway for the opposite limb. The impulses from these secondary neurones, on being transmitted up to the sensorium, are then interpreted as arising in the sound limb. If the excited internuncial neurones can give widespread inhibitory effects as well as excitatory, such inhibition of the secondary neurones relaying impulses from adjacent roots would account for "spreading hypoalgesia."

Dermatomes in a Case of Cauda Equina Injury.—It would seem that the chief reason why our observations on the fifth lumbar and first sacral dermatomes differ from those of Fœrster is that we employed a different criterion for sensory testing. Fœrster, like ourselves, used light pinprick, but he marked out areas of apparent analgesia, taking as his boundary the line at which an area without sensation changes to one of pain perception. We, however, mapped out areas of hypoalgesia, taking as our boundary the line of change between slightly impaired sensation and completely normal sensibility. Consequently our dermatomal areas are more extensive than his; and moreover we have been able to delineate areas of sensory impairment after a lesion of only a single nerve root, which would not have been possible had we adopted Fœrster's criterion.

We were fortunate in being able in a case of gunshot wound of the cauda equina to compare our method of sensory testing with that of Fœrster, and incidentally to substantiate the validity of many of the arguments we

have raised in the discussion. This patient, an unimaginative middle-aged man, had suffered a complete interruption of the fifth lumbar and all the sacral nerve roots on one side of his body. We were thus able to study the overlap between the fourth and fifth lumbar dermatomes. His injury had been caused sixteen months earlier by an 0·22 rifle bullet, which had penetrated his back in the midline between the third and fourth lumbar vertebræ, and had transversed the theca to lodge in the centre of the third lumbar intervertebral disc. The cauda equina had been explored a few hours after injury, and the roots of its left half were found to be intact, whereas those of its right half with the exception of the outermost one (presumably the fourth lumbar root) were severed.

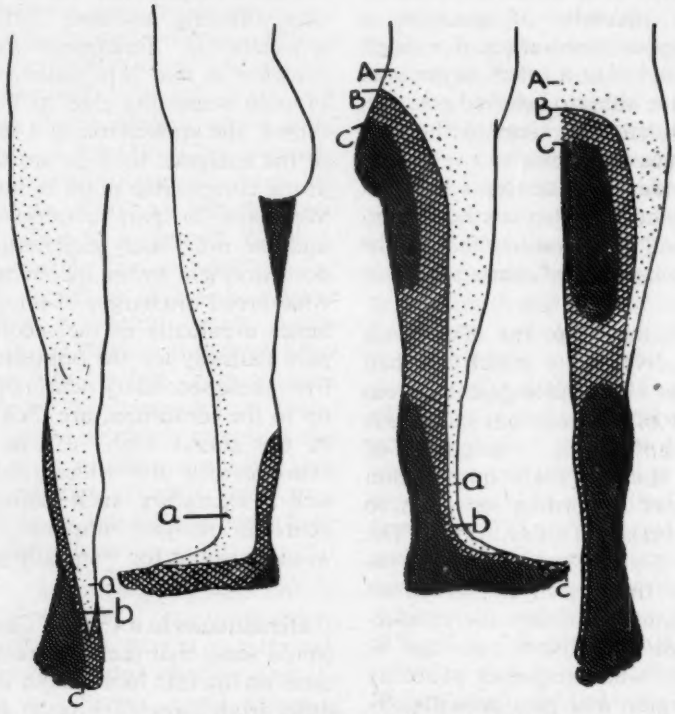

FIG. 10.—Diagram showing extent of sensory disturbance after section of fifth lumbar and all sacral nerve roots. Cross-hatching shows the area of loss of sensation to light pinprick. In the shaded area there was complete loss of sensation to massive pain stimuli. In the dotted area there was hypoalgesia.

When this man was tested with painful stimuli, three sensory levels could be made out (Fig. 10). When tested with light pinprick, an area of seemingly complete sensory loss (depicted by cross-hatching in Fig. 10) was found extending down the whole of the posterior aspect of the limb from the buttock in the midline above to the toes below. It embraced the outer two-thirds of the dorsum of the foot as well as the sole and inner border. When sensation was then retested with a disc of metal, heated sufficiently to cause a painful sensation without blistering on momentary application to the intact skin, the extent of the complete sensory loss was found to be much smaller (depicted in shade). It consisted of two areas, one in the buttock and the upper part of the thigh, and one in the calf, sole, and outer half of the dorsum of the foot, with an isthmus in between. Two similar areas of complete sensory loss were also found when sensation was tested with a heavy pinprick sufficient to draw blood. It was noteworthy that the lateral boundary of the upper area of complete analgesia lay from one and a half to two inches within the corresponding boundary for sensory loss to light pinprick, whereas the medial boundaries of the two areas corresponded closely. In the calf and foot the lateral and medial boundaries of the lower area of complete analgesia approximated to within half an inch of those of the area of sensory loss to light pinprick.

Next, sensation was tested with light pinprick in the same manner as we would have employed in a case of sciatica. In this particular patient we found that above and anterior to the area of sensory loss was an area of slight hypoalgesia (depicted by dotting). Its upper boundary ran along the iliac crest, wound round the front of the thigh, and then passed down the anteromedial

aspect of the leg towards the base of the great toe. The difference in feeling between this zone of hypoalgesia and the normal skin was very slight, but each time the testing needle crossed its boundaries the patient winced. We found no comparable zone of hypoalgesia on the medial side of the areas of analgesia.

This case therefore demonstrates clearly how, with painful stimuli of differing severity employed with differing criteria of sensory change, differing sensory levels can be made out. The area of sensory loss to light pinprick (depicted by cross hatching) corresponds closely to the territories of the fifth lumbar and all sacral nerve roots as described by Head. The demonstration that this area was really compounded of zones of deep hypoalgesia as well as of true analgesia supports our contention that, had Fœrster employed a more massive pain stimulus when investigating his areas of "remaining sensibility," he would have found that the fifth lumbar and first sacral nerve roots have a cutaneous representation in the thigh and buttock. Finally the zone of hypoalgesia above and anterior to the area of sensory loss corresponds exactly to the upper and anterior part of the fifth lumbar dermatome as observed by us in sciatica.

This case also demonstrates clearly how greatly the dermatomes overlap, and how this overlap is greatest in the thigh and buttock and is least in the leg and foot. As the fifth lumbar and all sacral roots had been severed, the lowest nerve root still subserving sensation was the fourth lumbar root. On reference to Fig 10, it can be seen that the boundary A-a of the zone of hypoalgesia represents the upper detectable limits of the fifth lumbar dermatome, for reasons discussed in the preceding paragraph; the boundary B-b of the area of sensory loss corresponds to the lower limit of the fourth lumbar territory, as Fœrster would have detected it by light pinprick; whereas the boundary C-c of the areas of true analgesia approximates more closely to the true lower limits of the fourth lumbar dermatome. The overlap of the fourth and fifth lumbar dermatomes would, therefore, seem to extend over at least three to four inches in the buttocks (from the points A to C), and only over an inch or less in the lower leg (from the points a to c). Thus, the various observations in this case of cauda equina injury substantiate most of the major premises which were raised in the discussion of dermatome hypoalgesia.

Conclusions

We therefore conclude that the various sensory disturbances, which occur in sciatica, originate in changes affecting a single dermatome, and can be explained by the hypothesis that each particular area of skin is innervated from two or more posterior nerve roots. These disturbances are seldom marked, and can only be detected by careful sensory testing. They result from lesions of either the fifth lumbar or the first sacral nerve roots, and conform to a pattern which is characteristic of the particular nerve root, and hence is of diagnostic value.

Our observation that a lesion of either of these nerve roots commonly produces a sensory disturbance, not only in the leg and foot, but also in the thigh and buttock, is of great importance. It casts doubt on the accuracy of the classical descriptions of the dermatomes and on the validity of the methods by which they were determined. From the clinical point of view, the disclosure of sensory impairment in the thigh and buttock in a patient with sciatica can no longer be necessarily regarded as evidence that several roots of the cauda equina are being involved, or that the patient is hysterical because his sensory pattern does not conform to the classical dermatomal charts, explanations which have both been often considered by clinicians in the past. It is our experience that if, in a patient with sciatica, a sensory disturbance—even though slight—can be demonstrated, careful plotting of its boundaries—especially on the dorsum of the foot, where the sensory changes are most readily detected—will usually afford a reliable indication as to the identity of the affected nerve root.

In this paper we have confined our observations to two dermatomes, the fifth lumbar and the first sacral, and have shown that they have a simple and orderly distribution extending the whole length of the lower limb, and one which is analogous to the accepted distribution of the dermatomes in the trunk. It seems unlikely that a similar arrangement should not occur with the other dermatomes of the limbs, both upper and lower. Clinical material exhibiting lesions suitable for the study of these dermatomes is sparse, but we have seen two cases of compression of the seventh cervical nerve root by an intervertebral disc protrusion, which exhibited sensory impairment extending the length of the upper limb from the fingers to the mid-dorsal region.

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AN OUTBREAK OF ATROPINE POISONING

BY

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FIFTEEN men, all Royal Air Force personnel, varying in age from nineteen to forty-two years, but mainly in the early twenties, were given a period of prolonged narcosis intended to last ten days in each case. They were all in satisfactory physical health but suffered from psychoneuroses.

The technique of treatment was a modification of that advocated by Brody (1940) for restless, older patients: 3 gr. of dial twice a day, together with paraldehyde in 3 drachm doses to a maximum of 9 drachms daily. To offset vomiting, 1 minim of liquor atropinæ is suspended in each 1·5 drachms of paraldehyde, thus giving a maximum of 6 minims of liquor atropinæ daily, which Brody states may be maintained for several days. He reported that fifteen of twenty-one patients vomited without atropine and only twenty-one of sixty-nine with atropine. From his description of the daily incidence of the minor complications which developed, it appears that vomiting, pyrexia, and albuminuria were evenly distributed throughout the treatment, whereas restlessness was more frequent in the second week, with fifty-three restless days to sixteen in the first week. The facts to be reported suggest that this restlessness is an atropine symptom, and it is possible that in some of Brody's cases more serious poisoning was escaped by a hair's breadth.

In this series, before some patients had finished the course and at the commencement of the treatment in others, the dose of atropine recommended by Brody was doubled because vomiting persisted. The doctor in charge of the treatment left before the narcoses were completed and the present writer took over, unfortunately unaware that any atropine was being used, and believing the drugs employed to be paraldehyde and dial only. As patients came out of the narcosis, several developed severe reactions and there appeared to be an epidemic of schizophrenia. Cases of atropine poisoning reported from time to time are usually concerned with the effects of a single large dose. Here the dosage was cumulative and spread over several days, and symptomatology was complicated by the simultaneous administration of large doses of dial and paraldehyde. The amounts of atropine taken are shown in the Table.

DOSAGE TABLE

	Case	Total Liq. atropinæ (in minims)	No. of days treated	Average daily dose (in minims)
Very severely affected	1	88	10	8·8
	2	84	10	8·4
Severely affected	3	56	8	7·0
	4	94	10	9·4
	5	96	10	9·6
Hallucinated	6	58	7	8·3
	7	68	10	6·8
	8	40	5	8·0
Unduly restless	9	66	10	6·6
	10	80	10	8·0
	11	50	6	8·3
Possibly showing atropine effects	12	58	7	8·3
	13	68	10	6·8
	14	42	5	8·4
	15	30	4	7·5

Combining these results with those previously reported by Brody, one can state tentatively that 6·0 minims of the liquor (equivalent to $\frac{6}{100}$ gr. atropine sulphate) can be given daily, for ten to fourteen days at least, without symptoms of any gravity developing, yet a dose of 8·8 minims (equivalent to $\frac{9}{100}$ gr. atropine sulphate) daily for ten days may endanger life. This is a very low margin of safety. A dosage of 94 minims (nearly 1·0 gr. atropine sulphate) in ten days produced severe symptoms, but with no threat to existence. The smallest total dose to produce hallucinosis was 40 minims.

Progress of the Narcosis

Taken on the whole, the progress of the narcosis was very smooth. Certain symptoms are described below, but they should be interpreted against the background of an easily manageable treatment. Only two patients vomited, one on the second day and another on the ninth and tenth days of

treatment. All patients had 6 gr. of dial every day, and the average daily dose of paraldehyde was about 9 drachms, the average sleep for the group being eighteen hours in every twenty-four. The average daily intake of nutrient fluid was 136 oz., and the average daily amount of urine excreted, excluding days when there was incontinence, was 87 oz. The blood pressure was taken daily and a typical variation was between 105 and 120 mm. Hg systolic, and between 60 and 80 diastolic. In one man only, when the blood pressure was 85 mm. Hg systolic and 50 diastolic, did symptoms of a minor collapse appear, but he responded well to treatment. One patient had retention which did not need catheterization, one patient had an attack of hiccoughs, and two complained of headache. One man made repeated complaints of chilliness. There were no high temperatures, but about half the patients recorded 99° F. or 100° F. on a few occasions.

These symptoms are common to prolonged sleep treatment. The following symptoms and signs, viewed in retrospect, are more likely to have been due to atropine.

Atropine Effects during Narcosis

The most striking and prominent effects were restlessness and a peculiar emotionalism. The restlessness was usually combined during the waking hours with frequent attempts to get out of bed, garrulity, and occasional noisiness and excitement. It was seen in eight cases, developing round about the sixth day or earlier and usually continuing to the end, being chiefly noticeable in contrast to the preceding apathy. Towards the eighth day increasing confusion and irrationality were occasionally noticed. The emotionalism was remarkable for the frequency with which it was associated with facile cheerfulness ; it was encountered in at least six men, in two of whom it increased to awkward hilarity. This good humour developed between the fifth and ninth days except in the two hilarious men (who were sometimes convulsed with laughter), in each of whom the symptom developed on the fourth day. In two cases fatuous amiability followed a few days of increased depression, and this in turn gave way before the end of treatment to a disgruntled humour with aggression and refusal of food. Three more cases cried at times after the sixth day, and two became anxious. It will be clear that it is impossible to separate these symptoms entirely from the effects of narcosis, but their frequency and the clinical impression suggest atropinism.

Of the customary signs of atropine poisoning, the increased pulse rate was masked during the course of treatment, presumably by the action of the sedatives. The only unusual feature was the fluctuation in individual rates, a typical swing being between 55 and 85 per minute, without apparent reason. Two days after the cessation of treatment the pulse rate was usually about 80 to 100. Towards the end of the course there was occasionally a slight increase in the average pulse rate, taking the mean of slowest and fastest ; for example in one case from 60, to 70, to 80 per minute on the eighth, ninth, and tenth days. A few patients were noticed to have dry and dirty mouths at the end of the treatment, but this was put down to the toxæmia of narcosis ; tongues were always moist from the second day after treatment. In two cases dilatation of the pupils was actually commented on at the bedside, but no significance was attached to this observation until it was recalled when atropine poisoning was diagnosed. In neither case was it continuous.

Two men complained of discomfort occasioned by a desire to micturate without being able to do so, and this has been described as an atropine effect (Clark, 1940). One man, who had slept about twenty-one hours daily for four days, only slept twelve hours daily during the next three days of treatment, although the dose of sedative was increased. The ward sister has since informed me that two men showed a hot, dry, skin for some days.

Progress after the Narcosis

The onset of the alarming aberrations occurred in a time sequence which was roughly similar in all those who developed urgent symptoms of acute mental disturbance. The first day after the suspension of treatment was reasonably quiet, but with a steady diminution of somnolence. During the second day the patient was wide awake, but disquieting behaviour was observed which rose to a peak during the third and fourth days, thereafter subsiding steadily. This finding is compatible with the comparatively rapid excretion of barbiturate and paraldehyde, leaving the more slowly excreted atropine to produce a purer effect.

The most striking early symptom was a pressure of talk accompanied by an irritable aggression and facile emotionalism, immoderate laughter being followed quickly by tears. Intermingled with evidence of increasing instability, there was a mixture of apprehension and anxiety. One patient revealed a hypomanic colouring in his symptoms, with flight and elation as well as volubility. On the fourth day after treatment this patient suddenly abandoned his unnatural good humour and became tremendously tense, excited, and pale with anger, speaking deliriously about the doctors and nurses. From the next day his excitement gradually subsided,

exhibiting periodic effervescence of a kind to be described in further cases. Even after a week his behaviour and manner were odd. After that he became the pleasantly mannered youth, with disguised anxiety symptoms and a history of several years of psychopathic behaviour, whom we had known before the treatment. Another very similar case was transferred to a military mental hospital as a case of catatonic schizophrenia. He made a good recovery.

Three patients complained of considerable depression after treatment and one, the only death, after asserting that his thoughts were being read, fell thirty-five feet from his bedroom window and was killed. This may have been an accident, and a desire for air, an awkward window, and giddiness may have been responsible. Suicide is more likely, and he may have killed himself either because of his depression or in order to escape from atropine hallucinosis.

Dreams and nightmares were fairly common, and hallucinations of smell, hearing, and sight were noted —poisoned food, fire, and electric currents being prominent. In these states the anxiety and fear already referred to were exaggerated. Sometimes the dreams were distorted versions of recent terrifying experiences, and they were then probably the outcome of the anxiety, being similar to nightmares often observed in traumatic anxiety states.

Three patients had a strong craving for a cigarette soon after treatment and one of them had a distressing longing for sexual satisfaction. Giddiness was fairly common and with the first cigarette was excessive. It is difficult to assess these cravings, although the marked giddiness was probably an atropine effect. Only two patients complained of unsteadiness of gait, and in one this persisted for three days, but patients were mainly confined to bed. The first bowel action was sometimes painful, and one man, who had been given a dose of cascara, described it as " the worst agony I have ever experienced." Four men complained of haziness of vision and inability to read or write. Three had headaches and spoke with difficulty, another could not find words, two were somewhat somnolent, and two commented on a sensation of peculiar blankness ; in these it is almost impossible to differentiate between narcotic and atropine effects.

The very limited pulse range has already been commented upon. During the first four days after treatment there was a steady increase in the extent and duration of dilatation of the pupils, but in every case the dilatation was periodic, alternating with periods during which the pupils returned to normal size.

One case (case 1 of the Table) will be described separately because of the extraordinary resemblance of the severe symptoms to insulin coma. This patient was aged 19 and was suffering from acute anxiety after operational flying. On the eighth, ninth, and tenth days of narcosis treatment he was noticed to be confused and irrational when awake, and to be talking much disconnected nonsense. On the first day after treatment he was quiet and confused, muttering from time to time, but nothing was observed that gave rise to any anxiety. During the next day he had periods of restless excitement and began to complain that he was influenced by the rays of a wireless set and by the electric lights which played on him. During the periods of excitement his pupils were widely dilated, and sweating was marked. He continued to take fluids freely.

On the third day his hallucinatory experiences increased and he demonstrated invisible wounds and wiped imaginary blood from various places. At this time his continuing attacks of excitement were marked by obvious terror and apprehension, and in his more lucid moments he mentioned his dreams, which recalled his flying experiences. Between attacks the pupils were small. The pulse rate fluctuated between 80 and 120 per minute. During the third night he became delirious during his periodic attacks, and his pulse rate rose to 160, the temperature to 101° F., and the respiration rate to 25 per minute. He coughed up a little sputum, but the lungs were clear and the urine normal. By this time atropine poisoning had been diagnosed, and he was given morphia 0·25 gr., oxygen inhalations, and coramine injections, as well as ordinary nursing attention. On the fourth day his condition became much worse and his life was despaired of. He had successive attacks of coma, with a tremendous rise in the pulse rate to 180, 200, and over, until it became thready and uncountable. Respiration was coarse and rapid ; the pupils dilated to the rims ; drenching sweat poured from him, and he went into tonic rigidity and opisthotonos, with his legs extended and the arms flexed across his chest. This state was followed by jactitation of arms and head, after which he gradually relaxed, the pupils diminished to normal size, and he regained consciousness, with the pulse rate slowing and strengthening, the excessive perspiration being the last abnormality to diminish. The symptoms were exactly like hypoglycæmic coma with adrenaline crises. He was treated for shock, with warmth, elevation of the foot of the bed, coramine, and oxygen. On the advice of Air-Commodore Conybeare, intravenous salines were given and salt added to the diet. The patient took fluids well in his quieter periods throughout.

During the fifth day he had four more attacks, but each was less in intensity than the one before and the pulse rate rarely exceeded 160 per minute. The last attack worthy of the name occurred on the sixth day. Thenceforward he gradually recovered, except that on the fourteenth day after the narcosis treatment he displayed acute panic reaction after severe pain in the left side of the chest, which he interpreted as a dangerous heart attack.

Discussion

Clark (1940) states that atropine paralyses parasympathetic nerve endings by inhibiting acetylcholine, and that it has a variable stimulating action on the sympathetic, largely masked by the dominance of the action on the parasympathetic endings. Moderate doses produce cerebral stimulation, and there is stimulation of the lower motor centres of the brain. The action is known to be prolonged.

The dose of the liquor is 0·5 to 1 minim, that is 1/200 to 1/100 of a grain of atropine sulphate ; 0·5 gr. has proved fatal, but, in a most exceptional

case, a dose of 15 gr. was survived. Susceptibility varies enormously. No case in this series had as much as 1 gr.

The acute signs and symptoms are dryness of the skin and secretions, dizziness, impaired vision, dilated pupils, and greatly increased pulse rate, with some increase in respiratory rate and a slight rise of temperature. Excitement, garrulity, and restlessness follow, and may lead on to delirium with hallucinations and finally coma. Epileptic attacks may occur, with paralysis of medullary centres. Munns (1929), writing of children under a month old, wonders if the heat-regulating centre is affected.

Young children are known to tolerate its action well, and sensitivity increases with age. Métivier (1935) describes an unusual reaction in a woman of seventy-four, who developed excitement and pleasing hallucinations after being given atropine eye drops. Carter (1940) describes the case of an old man of seventy-three who took 1·2 gr. of atropine. Treatment was not started for ten hours, when convulsions commenced. There was coma, dilated and fixed pupils, retention of urine, dry mouth, stertor, a rapid pulse, and spasticity and profuse perspiration. The spasticity is interesting in view of the rigidity in the attacks described above in Case 1 of the Table. Carter's patient was persistently trying to get out of bed and was hallucinated, picking at the bed clothes and later complaining of blurred vision. On the second day he was elated, excited, very talkative, and complained of headache. He had recovered by the fourth day. Concerning the variation in pupillary size, it is interesting to recall the findings of Levine and Schilder (1942) in catatonics. After the instillation of atropine they noted in a proportion of these an inconstancy of pupillary reaction to light and before fixation, suggesting an autonomic imbalance with parasympathetic dominance.

In view of the comparative smallness of the dose of atropine in the cases reported here, and the fact that the prescription was spread over a period of up to ten days, the conclusion can hardly be escaped that the narcotic not only masked the action of the atropine effectively, but also in some way reduced its excretion, so that at the end of treatment an effect was rapidly produced as if something like the total atropine given was acting as a single dose. There was no evidence of renal damage, but there may have been selective changes in kidney function. The striking nature of the parasympathetic—sympathetic swings, which gradually grew in intensity following the cessation of treatment, suggest a "blocking" of hypothalamic cells with dial, followed by a sudden invasion by atropine as the dial was excreted.

Mental illnesses indistinguishable from schizophrenia have been produced by the events here described. These cases closely simulated catatonic excitement, and four cases showed the almost pathognomonic "thought reading and influence by external agencies" of schizophrenia. Daube (1942) has described four cases of "pervitin" psychosis with a general picture of paranoid ideas, illusions, hallucinations, restlessness, irritability, and pronounced anxiety. Some patients were euphoric. These symptoms are similar to those described in the present paper, and suggest a non-specificity in the causal agents which, acting on cortex or midbrain, or both, can produce schizophrenia-like reactions. Ivy and Goetzl (1943) also have described the excitement produced by "pervitin," a benzedrine-like substance. The strong resemblance to schizophrenia produced by mescaline intoxication which was described by Stockings (1940) is closely paralleled by the cases described in this paper. The cortical effects of atropine must not be forgotten, but it is tempting to postulate that the dial facilitated a preponderating effect on the hypothalamus. The autonomic disturbances, and the unusual resemblance to insulin coma in one case, suggest a hypothalamic intoxication producing an illness indistinguishable from some forms of schizophrenia. Insulin acts primarily on the parasympathetic, presumably causing a pendulum over-action of the sympathetic and waves of adrenaline secretion. Here the parasympathetic may be paralysed, possibly freeing the sympathetic, or the actual hypothalamic cells may be disturbed in their action.

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THE EFFECT OF REINNERVATION ON COLLAGEN FORMATION IN DEGENERATING SCIATIC NERVES OF RABBITS

BY

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ONE of the phenomena of Wallerian degeneration in peripheral nerves is the formation of new endoneurial collagen. In a previous paper (Abercrombie and Johnson, 1946) we estimated the amount of collagen formed in degenerating sciatic nerves of rabbits during various periods up to two hundred days after the nerves had been severed. We found that significant amounts of collagen are formed during all periods of degeneration studied. The purpose of the investigation reported in the present paper is to determine whether reinnervation has any effect on this process of collagen formation. To that end we have compared the collagen content of completely severed nerves which undergo degeneration in the absence of reinnervation (these are referred to as non-reinnervated nerves), with the collagen content of crushed nerves which undergo degeneration but are very rapidly reinnervated (these are referred to as reinnervated nerves). One hundred days were allowed to elapse after the severance or crush before the nerves were removed for collagen estimation; a period during which an easily detectable amount of collagen is formed in normal degeneration.

Method

Our material consisted of the sciatic nerves of twelve adult rabbits, each providing one reinnervated and one non-reinnervated nerve. In each rabbit the sciatic nerve of one side was cut 1·5 cm. below the level of the third trochanter, and the central stump was sutured to the skin. The result of this procedure is Wallerian degeneration throughout the peripheral stump with little or no reinvasion by axons. The sciatic nerve on the other side of each rabbit was crushed with smooth-tipped forceps, also at 1·5 cm. below the level of the third trochanter. The effect of crushing in this way is to interrupt all nerve fibres (axonotmesis), and this is followed by rapid and complete reinnervation. The new axons enter the degenerated peripheral zone after a latent period averaging five days, and they extend throughout the region of nerve studied within about twenty-five days of the injury (Gutmann and others, 1942), and thereafter increase in diameter, reaching approximately one third of their normal volume at one hundred days, and their normal volume at about two hundred and fifty to three hundred days (Gutmann and Sanders, 1943).

One hundred days after the initial operation each animal was killed and part of each of its sciatic nerves taken for collagen estimation. The part of each nerve used for estimation consisted of the whole sciatic nerve in the thigh and knee peripheral to a point one-half cm. below the original crush or cut; together with the anterior and posterior tibial branches in the shank down to a level 3 cm. below the point of origin of the branch of the peroneal to the extensors of the shank.

After removal of the epineurium, the collagen content of the twenty-four nerves was determined simultaneously and under identical conditions by the method of Lowry and others (1941), and slightly modified as detailed in our previous paper (Abercrombie and Johnson, 1947). As in the experiments recorded in that paper, half the nerves were extracted in NaOH for twenty-four hours, and half for forty-eight hours.

For each nerve we obtained, as in our previous paper, estimates of the nitrogen content of the initial NaOH extract ("NaOH-soluble N"); of the supernatant after autoclaving ("collagen N"); and of the residue after autoclaving ("residue N").

The figures given in the Table are means of the absolute values for the standard length of nerve removed; and means of "pair-differences," a pair-difference being the value for the reinnervated nerve minus the value for the non-reinnervated nerve of each rabbit taken individually. It should be noted that in our previous paper we did not express the results of our analyses in absolute values, but in a standardized form. Since in that work each rabbit provided an undegenerated sciatic nerve as well as a degenerated one, we were able to express the estimates for degenerated nerve as mg. N per 100 g. wet weight of the equivalent length of undegenerated nerve, which is obviously not possible in the present work.

TABLE

	Wet weight	Collagen N	NaOH-soluble N	Residue N	Total N
Non-reinnervated nerves ..	93 ± 5	0·82 ± 0·05	1·21 ± 0·05	0·014 ± 0·002	2·04 ± 0·10
Reinnervated nerves ..	115 ± 5	0·87 ± 0·04	0·45 ± 0·04	0·047 ± 0·004	2·36 ± 0·08
Gain by reinnervation (pair-differences)	23 ± 6	0·05 ± 0·04	0·24 ± 0·06	0·032 ± 0·004	0·33 ± 0·10
Undegenerated nerves ..	82 ± 2	0·47 ± 0·01	0·92 ± 0·02	0·17 ± 0·01	1·56 ± 0·03

Mean values in mg. per standard length of nerve with standard errors

The proximal half-centimetre of the non-reinnervated sciatic nerve stump, and the posterior tibial nerve of the reinnervated sciatic distal to the region used for collagen analysis, were fixed and stained by Bodian's method for axons. Most of the non-reinnervated stumps were devoid of axons, though there were a few stray ones in three of them. All the reinnervated stumps contained numerous well-developed axons.

As a check on the consistency of our method of estimation, it is important to compare the values obtained for the set of 100-day non-reinnervated nerves in this experiment with the values independently obtained for similar nerves reported in our previous paper (Abercrombie and Johnson, 1946). The analyses recorded in the present paper were done in one simultaneous batch, while those recorded in the previous paper were made at several different times. In the previous paper, as stated above, the N contents and wet weights were expressed in a different way from that used here. But since on the average the same amount of nerve was removed from each rabbit in the two experiments, the mean absolute values (not published in the previous paper) can be directly compared. That we were successful in removing a well-standardized amount of nerve is shown by the fact that mean wet weight and total N content do not differ, within our limits of accuracy, between the two sets of 100-day degenerated nerves. The collagen N is rather lower, and the NaOH-soluble N rather higher in the earlier set of nerves, but these differences are not significant ($P=0{\cdot}1$ in both). The residue N, however, is almost twice as high in the earlier set of nerves, and the difference is significant ($P=<0{\cdot}01$). The consistency of the method is, therefore, satisfactory except in the case of the residue N, which is a very small fraction of the total N. Consistency of estimates of residue N within a single batch of simultaneous analyses is good, as the standard errors in the Table show; but different batches differ rather disconcertingly from each other.

Results

In the Table we give the mean wet weight of the standard length of nerve analysed, and the mean N content of each of the different fractions investigated, with their respective standard errors. The final column, "Total N", is the sum of the three preceding columns, and, as explained in the previous paper, falls a little short of the real total N since lipin N is only partly estimated. In the upper row is the mean value of the twelve non-reinnervated nerves; and in the second row that of the twelve reinnervated nerves. The third row gives the mean of the pair-differences, each pair-difference being obtained by subtracting, for each pair of nerves, the non-reinnervated value from the reinnervated value. The fourth row gives for comparison mean values for thirty-three normal undegenerated nerves (from data used, in a different form, by Abercrombie and Johnson, 1946). The mean value for the reinnervated nerves is higher than that for the non-reinnervated nerves, in every column of the Table. The pair-differences for wet weight of nerve, NaOH-soluble N content, residue N content and total N content, are significantly different from zero by t test ($P=<0{\cdot}01$ in each case). The difference in collagen content is, however, quite insignificant ($P=0{\cdot}25$).

Discussion

In our previous paper (Abercrombie and Johnson, 1946) we showed that significant amounts of collagen are formed in the sciatic nerve during the first fifty days of degeneration and between fifty and a hundred days. Some collagen is probably also formed during the first twenty-five days. The indications are that collagen formation goes on continuously throughout the first hundred days of degeneration (excluding probably the first few days after severance, when the phenomena of degeneration have hardly appeared); and, once started, the rate of formation does not seem to change greatly during this period. We have now found that one hundred days after division a nerve has the same collagen content whether or not it has been reinnervated.

We presume, therefore, that the whole process

of collagen formation proceeds, regardless of whether reinnervation takes place or not, for at least the first hundred days after division of the nerve. Collagen formation during Wallerian degeneration when reinnervation is prevented continues, of course, well beyond one hundred days (Abercrombie and Johnson, 1946), and we cannot deny that beyond a hundred days reinnervation may modify the process of fibrosis. But the surprising absence of any demonstrable effect during the first hundred days suggests that a later effect is not likely to be important.

The other components (NaOH-soluble N, residue N, and also wet weight), investigated incidentally to the determination of collagen content, are distinctly different in the reinnervated and non-reinnervated nerves. It is not that there is a general tendency for the composition of a reinnervated nerve to approach that of an undegenerated nerve (see Table). It seems to be rather that a reinnervated nerve represents, in weight and chemical composition, a degenerated nerve with new nerve-fibres superimposed. If further work can establish this, the way is open to a quantitative analysis of the growth of new axons during the process of reinnervation. Assuming the point for the present, the pair-differences in the Table represent quantities of nerve-fibre material formed during one hundred days in the particular length of nerve used. It appears that the new nerve-fibre material has a lower N content relative to its wet weight than the rest of the nerve (1·4 per cent. of wet weight for the nerve-fibres, against 2·2 per cent. for the non-reinnervated nerve), but this conclusion is, of course, tentative.

As to the vexed question whether Schwann cells or endoneurial fibroblasts are responsible for collagen formation in peripheral nerves, our results give no conclusive answer. But they might be taken to give a little support to the view that endoneurial fibroblasts are implicated. Reinnervation involves the development of an intimate association between Schwann cells and axons. In some respects this is known to affect the Schwann cells profoundly, switching them on to myelin production (see Speidel, 1933) and inhibiting their powers of migration in tissue culture (Abercrombie, Johnson, and Thomas, unpublished). The endoneurial cells, on the other hand, do not come into contact with the new axons, and they are not known to be affected by reinnervation in any way. The absence of an effect of reinnervation on collagen formation, therefore, parallels the absence of any known effect on endoneurial cells, but does not parallel the existence of a profound effect on Schwann cells.

It should be noted that there is no sign of the fibrosis-inhibiting substance which Weiss (1943) has suggested diffuses centrifugally along a nerve. The crushed nerve, which is left in continuity with the undamaged central stump and with the central nervous system, would, according to Weiss's suggestion, be expected to undergo some inhibition of fibrosis in comparison with the cut nerve, unless the crushed region prevents the centrifugal flow entirely, which seems unlikely. In fact there is no demonstrable inhibition of fibrosis in the crushed nerve.

Holmes and Young (1942) and Sanders and Young (1944) found that during prolonged degeneration the Schwann tubes of the peripheral stump of a severed nerve shrink considerably; and that when such a stump becomes reinnervated, the shrunken tubes fail to expand again to their original size. They suggested that the collagen formed in a peripheral stump during its degeneration might be responsible for limiting re-expansion. On the other hand *early* reinnervation, after a brief period of degeneration, leads to the reconstitution of a much more normal tube size (Sanders and Young, 1944). Although it seems entirely reasonable to suppose that new collagen prevents expansion after late reinnervation, the larger tube expansion which follows early reinnervation is not easy to explain. It is clear from our results that the difference in ultimate tube size according to time of reinnervation is not due to any inhibition of collagen formation by reinnervation. The difference is probably due to the outward pressure of the growing axons being exerted, in the case of late reinnervation after most of the collagen has been formed, and in the case of early reinnervation almost throughout the period of collagen formation. When the latter happens, the early expansion is opposed by only small amounts of new collagen; and when more collagen has formed the tubes have already partly expanded and need to stretch the more recently formed collagen relatively little in order to reach normal tube diameter.

Summary

Estimates have been made, by a chemical method, of the collagen content of rabbit sciatic nerves peripheral to a point where their nerve fibres had been experimentally interrupted a hundred days earlier in one of two different ways: (*a*) by complete severance of the nerve, preventing reinnervation, (*b*) by crushing, permitting rapid reinnervation.

There was no significant difference in collagen content between the reinnervated and the

non-reinnervated nerves. The process of collagen formation set going by interrupting a nerve is apparently uninfluenced by reinnervation.

Wet weight and non-collagen N were higher in the reinnervated nerves, the difference probably representing approximately the material of the new nerve fibres.

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